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Eric S. Krage

Date: _____

Biokinetics of Strontium-90 in Nonhuman Primates

By

Eric S. Krage

A dissertation

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To the Graduate Faculty

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Success is not final, failure is not fatal: it is the courage to continue that counts.

--Winston Churchill

Do not go gentle into that good night, Old age should burn and rave at close of day; Rage, rage against the dying of the light.

--Dylan Thomas

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ABSTRACT

Biokinetic models provide a mathematical means of predicting the distribution, retention, and clearance of contaminants within the body. The International Commission on Radiological Protection (ICRP) has recommended a systemic model for the assessment of strontium intakes. The latest revision provided in publication 78 is the current model used in the United States for strontium kinetics. Due to the inability to test on human subjects the need arises to analyze animal data using the prescribed models. This research aimed to examine the translocation of strontium in nonhuman primates using the ICRP 78 model. This effort led to the development of three strontium systemic models that could be used as a supplement to the existing ICRP 78 model that would support intakes in nonhuman primates. The developed models focused on pharmacokinetic modeling of bone seeking agents and the ion exchange of strontium with calcium in the bone apatite. Both male and female cohorts were examined using data collected by Dr. Patricia Durbin at Lawrence Berkley national laboratory. In addition, an investigation was made into the placental transfer of strontium from the mother to the fetus. As a result of the offspring analysis, it was determined that new models may need to be adopted in order to account for the transfer of strontium to the fetus from mothers for exposures prior to conception. Furthermore, the proposed nonhuman primate model was incorporated with the ICRP 30 gastrointestinal tract model to verify its efficacy. This research led to the development of a simplified nonhuman primate biokinetic model and included a modification of the strontium systemic model that incorporated simplified physiologically based improvements which were required based on the available data.

Chapter 1 INTRODUCTION

1.1 Problem Statement

The determination of internal doses is an essential component of individual monitoring programs for workers. It may also be needed for members of the public, who may have intakes of radionuclides in nuclear medicine or following accidental release of radionuclides into the environment. Assessment of internal hazard can be understood by knowing two key pieces of information; number of transformations and energy emitted per transformation. To assess the internal dose several key pieces of information are needed: amount of radioactive material in the body, in body organs, or in wounds by direct measurement and/or indirect measurement such as *a prior* knowledge of air concentration or excretion analysis; interpretation of monitoring data in terms of intake and/or internal dose by taking into account many influencing factors, such as physical and chemical speciation, route of intake, biokinetic and energy absorption processes (Doerfel H., 2002). In the second phase of interpreting bioassay measurement it is important to take note that there are a number of variables and uncertainties involved. Although the International Council on Radiation Protection (ICRP), International Atomic Energy Agency (IAEA), and National Council On Radiation Protection (NCRP) have published extensive tables to calculate dose per unit intake, these are default values based on assumptions related to the behavior of a reference person about the intake and physiological parameters that may not be valid in every situation. Determination of intake and the resulting internal dose may, therefore, be performed in many different ways

depending on the amount and quality of data, skills of the individual interpreting the data, computational tools available, and assumptions made.

1.2 Strontium In the Environment

Strontium is found in nature as a soft metal; radioactive ^{90}Sr is an anthropogenic nuclide generated as a byproduct of nuclear fission reactions with a yield of approximately 7% (EPA, 2012) (IAEA, 2008). The radioactive progeny is purely a byproduct of the fission process. It was largely dispersed in the 1950s and 1960s owing to atmospheric testing of nuclear weapons. The global strontium-90 cumulative distribution reached a peak in 1966 of approximately 500 PBq of material from nuclear weapons testing. Other significant sources of ^{90}Sr in the environment include the fire at the Chernobyl nuclear power plant in 1986 which regionally dispersed 125 PBq of ^{90}Sr into the environment and Fukushima Dehachi which released material regionally in Japan and into the Pacific Ocean (UNSCEAR, 2000) (UNSCEAR., 2015). It should be noted no formal report of the "other" potentially significant radionuclides (such as isotopes of strontium and plutonium) has been published on the source term for releases to the atmosphere from the Fukushima incident (UNSCEAR., 2015). Since its peak activity in the environment in 1966, the amount of radiostrontium has slowly decayed with a half-life of 28.79 years. Current measurements show that the current abundance of ^{90}Sr in the environment is very low. Two surveys have reported the strontium content in urban air to range from 4 to 100 ng/m^3 and average 20 ng/m^3 (Dzubay, 1975). Concentrations in Illinois were measured to be between 0.9 to 4.8 ng/m^3 between 1985 and 1988 for naturally occurring strontium (Sweet, 1993). The concentrations of strontium in the free air are generally higher near coal fire plants, where stable strontium is a gaseous product

released within the stack emissions (ATSDR, 2004). Current global distribution from the testing of nuclear and the Chernobyl incident can be calculated to be approximately 140 PBq (ZR, 1988).

Strontium in the environment includes both stable and radioactive compounds. When it is encountered in the air are it is typically present as dust. Clearly, most of the strontium in air is in the form of stable strontium. Very small dust particles of strontium in the air fall out of suspension and into surface water, onto the leaves of plants, and they are directly deposited in the soil. Frequently the deposition of strontium aerosols is associated with precipitation events such as rain or snow fall. Deposited particles of strontium eventually end up back in the soil or in the sediments of lakes, rivers, and ponds where they mix with other material. Most forms of stable and radioactive strontium are eventually dissolved in water. The source of stable strontium dissolved in water primarily comes from strontium in rocks and soil that water runs over and through. Only a small part of the strontium found in water is from the settling of strontium dust out of the air.

Storage of Strontium-90 in the soil regardless of the source of generation is typically disposed of in soil seepage pits, lagoons, or cribs. Storage of radioactive strontium is often under highly alkaline conditions (PH > 12) where ^{90}Sr solubility is low and its adsorption to surrounding soil is high. As natural weather returns these soils to near-neutral or slightly acidic conditions, the adsorbed and precipitate calcium and magnesium phases, in which ^{90}Sr is carried, change significantly in both nature and amounts (Spalding BP, 2001). This return to acidic conditions allows the strontium to begin to exchange more readily with the soil and slowly diffuse throughout the

environment. Radioactive strontium as produced in the fission process prior to treatment only occurs in one valence state (II). It does not form strong organic or inorganic complexes and is commonly present in solution as Sr^{2+}. The concentration is rarely solubility limited in soil or groundwater systems because the solubility of common phases is relatively high (Lefevre F, 1993). The concentration of strontium in solution is commonly controlled by sorption and ion-exchange reactions with soil minerals. This ion-exchange reaction allows the strontium to be able to be taken up into vegetation. Once entering the food chain it can later be consumed by humans.

1.3 Strontium In the Body

As an alkaline earth element, strontium follows the calcium pathway in the body much like lead, however, each element may exhibit different transfer rates. Once in the transfer compartment (Blood) of the body, strontium and calcium have similar kinetics and are rapidly translocated to the bone. Within a few months, nearly all the activity in humans is associated with the bone compartments (ICRP., Publication 67: Age-dependent dose to members of the public from intake of radionclides: part 2, ingestion dose coefficients, 1993). Since strontium is taken up primarily into the bone, the bone itself and nearby soft tissues may be damaged by cumulative exposure over time. The most detrimental effect takes place within the red bone marrow effecting the production of healthy red blood cells and bone regeneration. Strontium is of increased concern because it cannot be selectively removed from the body due to chelation or any other current type of medical intervention. Therefore, strontium continues to affect the body throughout the life of the exposed individual (Dojindo, 2015)

The ^{90}Sr activity entering through the respiratory tract or gastrointestinal tract is ultimately transferred to the blood and is retained by bone and soft tissues. The Human Respiratory Tract Model (HRTM) is represented by 5 anatomical regions divided up based upon differences in radio-sensitivity, deposition, and clearance the extrathoracic (head and neck) airways (ET) are divided into ET_1 the anterior nasal passage, and ET_2, which consists of the posterior nasal and oral passages, the pharynx and larynx (ICRP-, 1994). The thoracic regions (lungs) are Bronchial (BB, 1-8), Bronchiolar (bb), and Alveolar Interstitial (AI) also known as the gas exchange region. The lymph nodes in the lungs are associated with the extrathoracic and thoracic airways (LN_{ET} and LN_{TH}) respectively represented in Figure 1. Once a particle is inhaled, it enters the anterior nasal and nasorpharynys/larynx regions where it has four possible fates it may be; expelled back into the environment, be sequestered into the airway passage, caught in the mucous lining of the nasal region and swallowed, or be introduced into the bronchi region of the lung. If the particle is brought into deeper regions of the lung namely Bronchi, Bronchioles, and Alveolar interstitial regions, it may undergo absorption into the blood. Blood absorption in the lung is a two-stage process: dissociation of the particles into material that can be absorbed into blood (Dissolution); and absorption into the blood of soluble material dissociated from particles (uptake). Both stages can be time dependent and may be simplified as a two compartment model that translocates material into the blood compartment. The simplest representation of time-dependent dissolution is to assume that a fraction (f_r) dissolves relatively rapidly, at a rate s_r, and the remaining fraction ($1-f_r$) undergoes a slower dissolution, at a rate s_s. Uptake of the rapidly dissolved material is treated as an instantaneous injection into the blood. Its sometimes becomes

necessary to model for a significant fraction of material as slowly absorbed into the blood. To enable this to scenario, the ICRP HRTM model includes compartments in which activity may be retained in each region in a "bound" state. However, it is assumed by default that an inhalation uptake is instantaneous, and the bound state is not typically included unless specific information is known about the particles insolubility in the lungs. This insoluble material may become permanently sequestered in the lungs or brought up the mucociliary escalator and into the gastrointestinal tract.

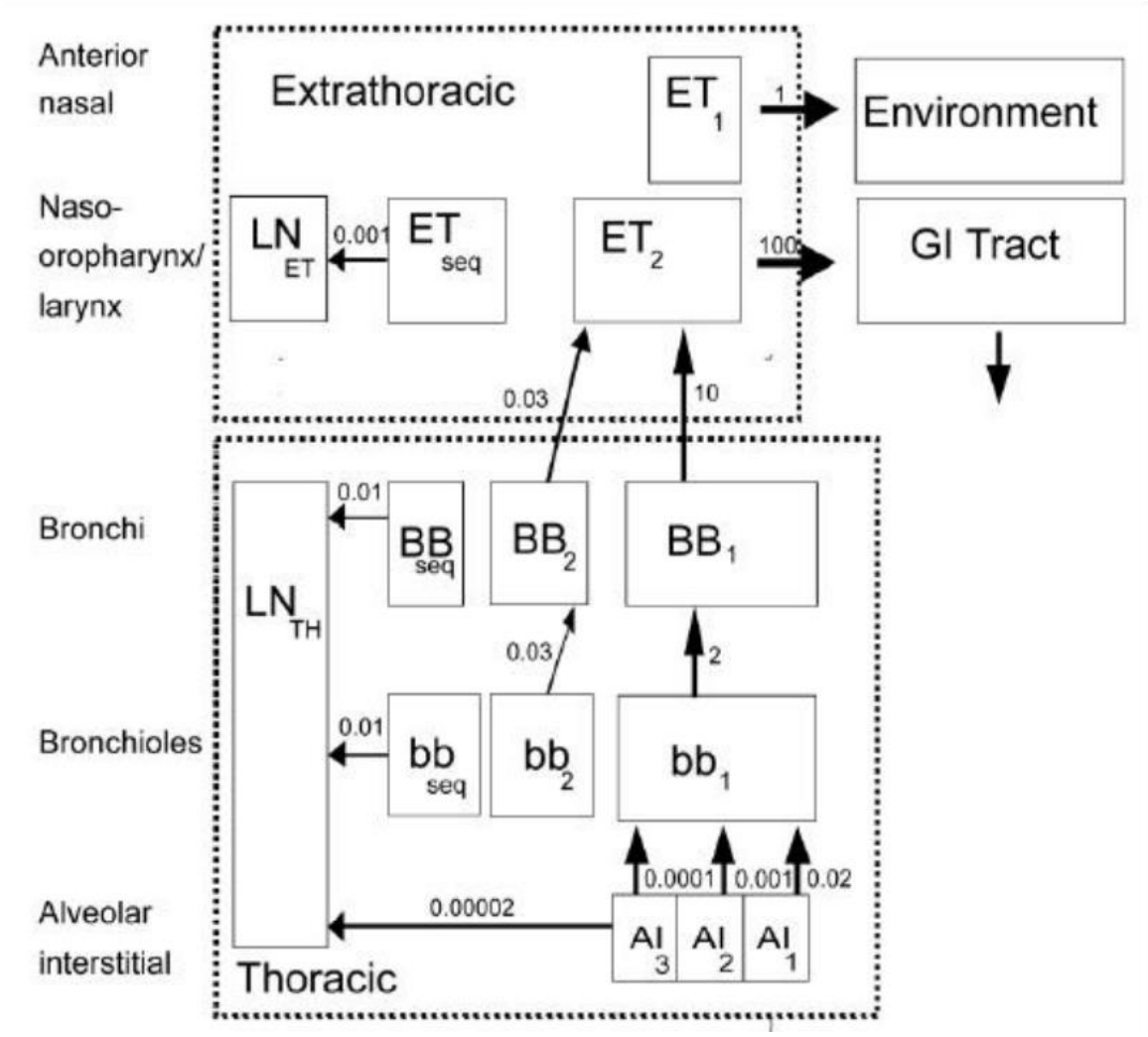

Figure 1 ICRP 66 Lung Model (ICRP-, 1994)

The current United States (US) regulatory model for calculating uptake and determining dose through ingestion is the ICRP 30 Human alimentary tract model. Once material enters the gastrointestinal tract (GI), it goes through four major compartments before material is expelled or absorbed (ICRPa, 1979) (ICRP, Publication 130: Occupational Intakes of Radionuclides: Part 2, 2015). In the ICRP 30 model, material enters into the stomach and then is transferred to the small intestine where it can be transferred to the blood (Transfer Compartment) or upper large intestine as seen in Figure 2. Once in the upper large intestine, material travels to the lower large intestine followed by excretion through the urine or feces.

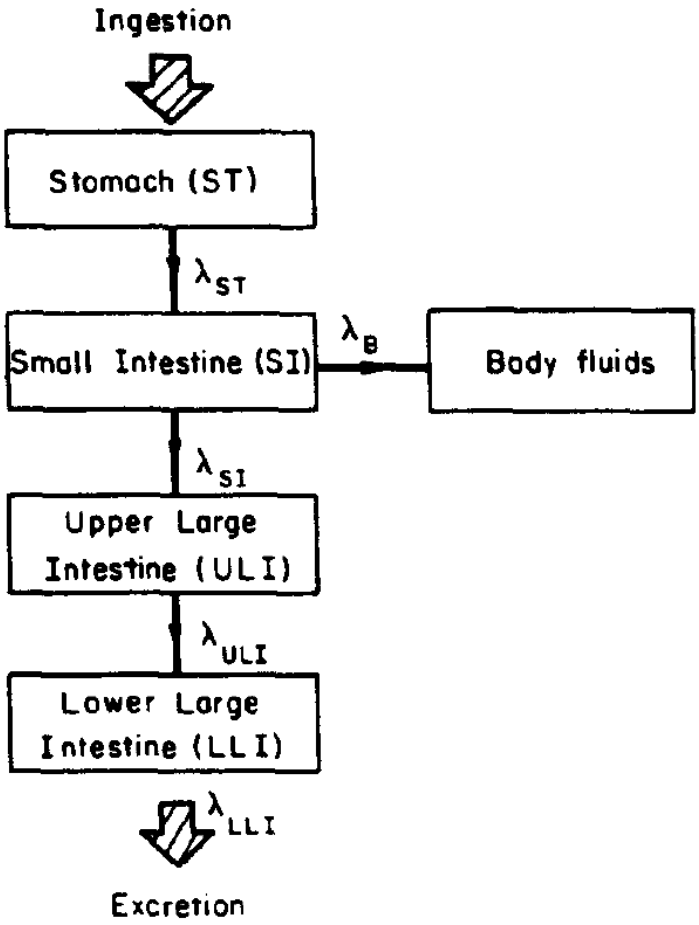

Figure 2 ICRP 30 Human Alimentary Tract Model (ICRPa, 1979)

The material now in the blood stream behaves according to the biokinetics of the specific elements. Strontium behaves similar to calcium and is considered to be rapidly exchangeable with bone material. The rapidly exchangeable activity once in the transfer compartment is circulated throughout the body and is partially excreted in the urine and feces (ICRP, 69, 1995). Over time, the rapidly exchangeable activity is transferred into the bone surfaces and finally to the non-exchangeable bone volume. The ICRP 1990 model (Figure 3) is intended to provide reasonably accurate predictions of the time dependent activity of strontium isotopes deposited on bone surfaces and within the

skeletal system, as well as rates of excretion after transfer into systemic body fluids (ICRPc, 1997).

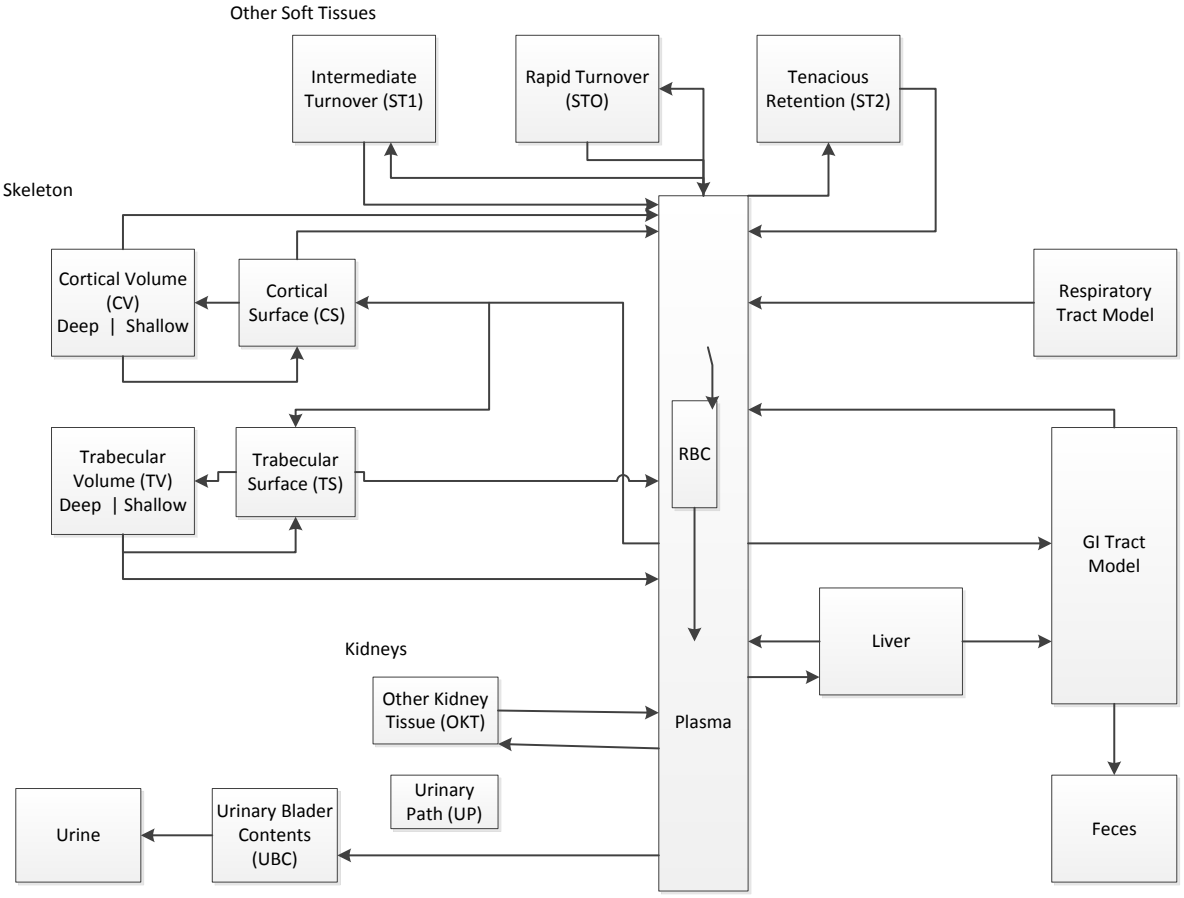

Figure 3 Compartmental Model for Ca-Like Elements "Strontium". (ICRPc, 1997)

1.4 Nonhuman Primates in Research

Rhesus macaque (Macaca *mulatta*) monkeys are one of the most extensively studied nonhuman primates. They have a broad geographic distribution second only to humans (MonkeyWorlds, 2015). Because of their anatomical and physiological

closeness to humans, the relative ease at which they can be maintained and bred in captivity, and the available supply from India, Rhesus *macaques* have long been the nonhuman primate of choice on which to conduct research on human and animal health-related topics (Mitruka, 1976). The rhesus and humans are known to share a common ancestor from 25 million years ago (Gibbs R, 2007). The rhesus macaque genome has a 93% genomic match with that of humans. Because of the rhesus macaques genomic similarities to humans and physiological characteristics, rhesus macaques are often used for biokinetic studies with radionuclides. Rhesus monkeys are also highly sought after for their similar gestation cycle to that of humans which takes place over a shorter time period 164 days compared to 280 days (Madison, 2011).

1.5 Purpose of the Study

The main purpose of this study was to develop a strontium biokinetic model in nonhuman primates (NHP) that could be used to test ancillary intake models that may ultimately be used in humans. The development of these models was based upon an investigation of the current ICRP publication 78 strontium systemic model and other bone seeking materials. Preliminary work demonstrated that the current ICRP 78 systemic model as it stands does not predict activity residing in the body well for nonhuman primates. To test the ICRP 78 strontium-90 systemic model, nonhuman primate bioassay data generated at Lawrence Berkeley Laboratory from 1959 through 1982 by Durbin et al. was analyzed. A group of eight male subjects that had been injected with the same activity was used to generate a composite data set to evaluate the ^{90}Sr biokinetic model. Along with the ICRP model, three models developed by Krage et

al. were also analyzed (Krage ES, 2016). After evaluation of the three models, one model (Model C) was determined to describe the kinetics more accurately than others. Using the Model C biokinetic model as determined by the male nonhuman primate study conducted, a dataset from a group of female nonhuman primates were composited and analyzed. Preliminary analysis of the composite female cohort data suggested that systemic model parameters may be modified in order to develop a more representative systemic model for female NHP's. Additionally, it was of interest when evaluating these females to consider the transfer of radiostrontium to the fetus from mothers injected with radiostrontium to evaluate the efficacy of ICRP 88 predictions.

The ^{90}Sr-NHP models were developed using a composite cohort of male and female monkeys. Test models were subsequently tested using other nonhuman primate subjects from the Durbin study not used in the model development (test subjects). The test cohort consisted of 4-male test cases and 6-female cases. As a secondary goal, this research reviewed the physiological process of intake through the gastrointestinal tract using the ICRP 30 model as described by retention in the skeleton. Prediction capabilities of the ICRP 30 gastrointestinal tract model paired with the strontium NHP models were analyzed to assess if improvements in the GI tract model could be experienced.

1.6 Hypothesis Testing

The robustness of the ^{90}Sr systemic model was evaluated by the following *a priori* hypotheses:

$H_{1,0}$: The ICRP Report No. 78 systemic model for ^{90}Sr will not accurately predict the intake from composited primate bioassay data.

$H_{1,A}$: The ICRP Report No. 78 systemic model for ^{90}Sr does accurately predict the intake from composited primate bioassay data.

The null hypothesis will be accepted if the predicted and injected Sr^{90} activities are within 10% of one another. In the event that a larger deviation occurs, the null hypothesis will be rejected in favor of the alternate hypothesis. Support of the null hypothesis suggests that the intake prediction cannot be scrupulously predicted by the default model parameters.

The predictive capabilities of the suggested ^{90}Sr systemic models will be evaluated by the following hypotheses:

$H_{2,0}$: Models A, B, and C cannot be altered to improve the predicted composited skeletal bioassay data of ^{90}Sr in Male Macaque monkeys.

$H_{2,A}$: Default transfer rates as specified by Models A, B, and C can be altered to improve the predicted composited skeletal bioassay data of ^{90}Sr in Male Macaque monkeys.

The null hypothesis will be accepted if the predicted and injected ^{90}Sr activities are not 10% more accurate than the default prediction. In the event a smaller deviation occurs the null hypothesis will be rejected in favor of the alternate hypothesis. The acceptance of the alternate hypothesis suggests that the skeletal prediction cannot be accurately predicted by the current model.

The predictive capabilities of the suggested ^{90}Sr Model C will be evaluated by the following hypotheses:

$H_{3,0}$: Models C cannot be altered to improve the predicted intake of ^{90}Sr in the composite cohort of Female Macaque monkeys.

$H_{3,A}$: Default transfer rates as specified by C can be altered to improve the predicted intake of ^{90}Sr in the composite cohort of Female Macaque monkeys.

The null hypothesis will be accepted if the predicted and injected ^{90}Sr activities are not 10% more accurate than the default prediction. In the event a smaller deviation occurs the null hypothesis will be rejected in favor of the alternate hypothesis. The acceptance of the alternate hypothesis suggests that the skeletal prediction cannot be accurately predicted by the current model.

The predictive capabilities ^{90}Sr NHP systemic models paired with the ICRP 30 gastrointestinal tract will be evaluated by the following hypotheses.

$H_{4,0}$: Optimized transfer rates for Male and Female NHP systemic models and ICRP 30 cannot be used to predict ^{90}Sr ingestion in Macaque Monkeys.

$H_{4,A}$: Optimized transfer rates for Male and Female NHP systemic models and ICRP 30 may be used to predict ^{90}Sr ingestion in Macaque Monkeys.

The null hypothesis will be accepted if the predicted and injected ^{90}Sr activities are not 20% more accurate than the default prediction. In the event a smaller deviation occurs the null hypothesis will be rejected in favor of the alternate hypothesis. Support of the alternate hypothesis suggests that the intake prediction cannot be improved by the current model.

Chapter 2 BACKGROUND

2.1 Characteristics of Strontium-90

Strontium-90 is of radiological concern due to the energy of its radiation, relatively long half-life, and high yield in the fission process. The ease of strontium's mobility through the environment and its radiological properties led it to being classified early in its discovery as one of the most hazardous nuclear fission byproducts. Strontium-90 is produced in the fission process with a yield of approximately seven percent. It has been introduced into the environment by nuclear weapons tests and nuclear power accidents (Glasstone & Dolan, 1977). ^{90}Sr is has a half-life of 28.79 years and upon its decay undergoes isobaric transition emitting a particle with an average energy of 0.2 MeV. The decay product; ^{90}Y which is normally found to be in secular equilibrium with ^{90}Sr also undergoes isobaric transition ultimately emitting a beta particle of 2.28 MeV (max). The radionuclide ^{90}Y decays to stable ^{90}Zr with a halftime of 64.10 hours, Figure 4.

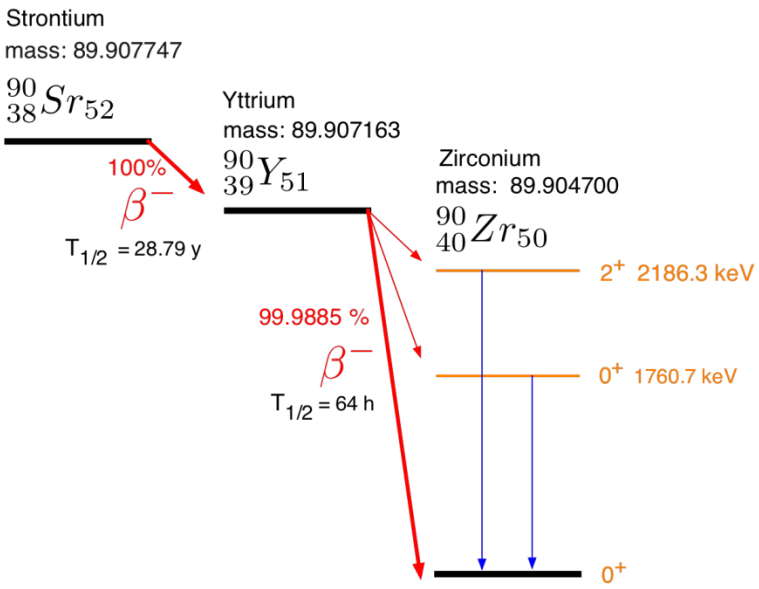

Figure 4 ^{90}Sr Radioactive decay scheme

2.2 Developmental Biology of Bone

Strontium a known bone seeker is most detrimental to an individual when bone is rapidly building. This produces a problem that is most apparent during the stages of fetal development. The process of transfer of nutrients and material may be transferred from the mother to the fetus through the model shown in Figure 5 is specific to calcium and its cogners. Radioisotopes of elements or radiocogners of these elements that are required by the developing embryo/fetus will follow normal pathways through maternal blood. The processes involved in transferring material from the maternal reservoir to the fetal blood through the placenta include simple diffusion, facilitated transport, and active transport, movement through pores and channels, and pinocytosis.

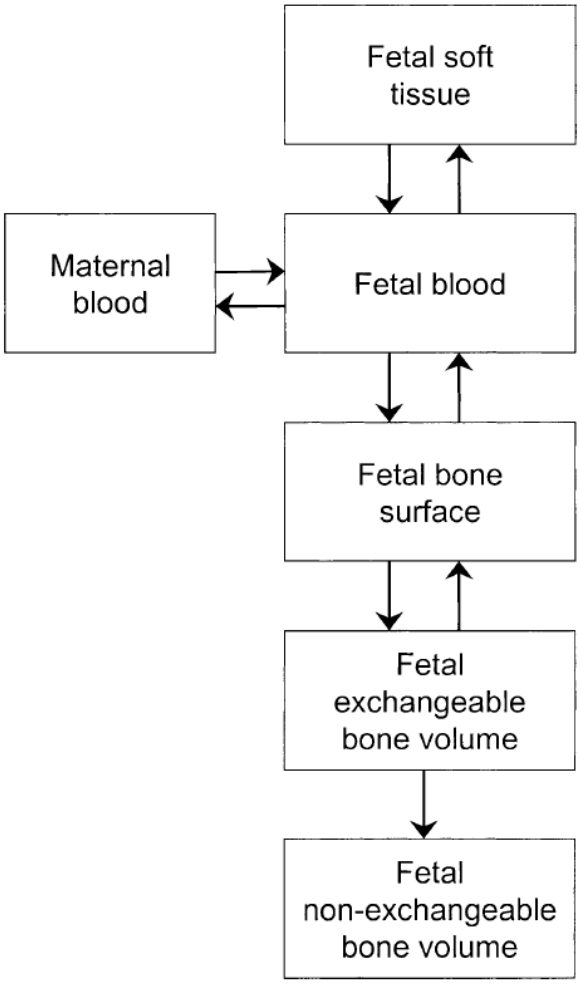

Figure 5 Biokinetic model for alkaline earth elements in the fetus

The precursor to bone is cartilage formation, in which mesenchymal cells become closely packed, become chondroblasts, and secrete extracellular material containing different amounts of collagen fibers. The cartilage then forms into the shape of the bone it is to represent. Enlarged chondroblasts subsequently secrete alkaline phosphates which leads to the local calcification of the matrix. Chondroblasts then die leaving spaces that are invaded by osteoblasts, which lay down layers or lamella of bone. This process continues in both directions from the central region with calcified cartilage being replaced by bone lamella and new cartilage being formed at the ends. As the lamellae are

formed, some cells remain between layers, now called osteocytes, connected by processes running through canaliculi in the bone matrix as shown in Figure 6. As well as bone formation, bone growth and remodeling requires considerable removal or resorption, which is performed by osteoclasts. Cavities formed within the bone become filled with the haemopoietic tissue of the red bone marrow, also of the mesenchymal origin. Bone growth and ossification are particularly rapid during the first weeks of the fetal period (Carlson BM, 1994).

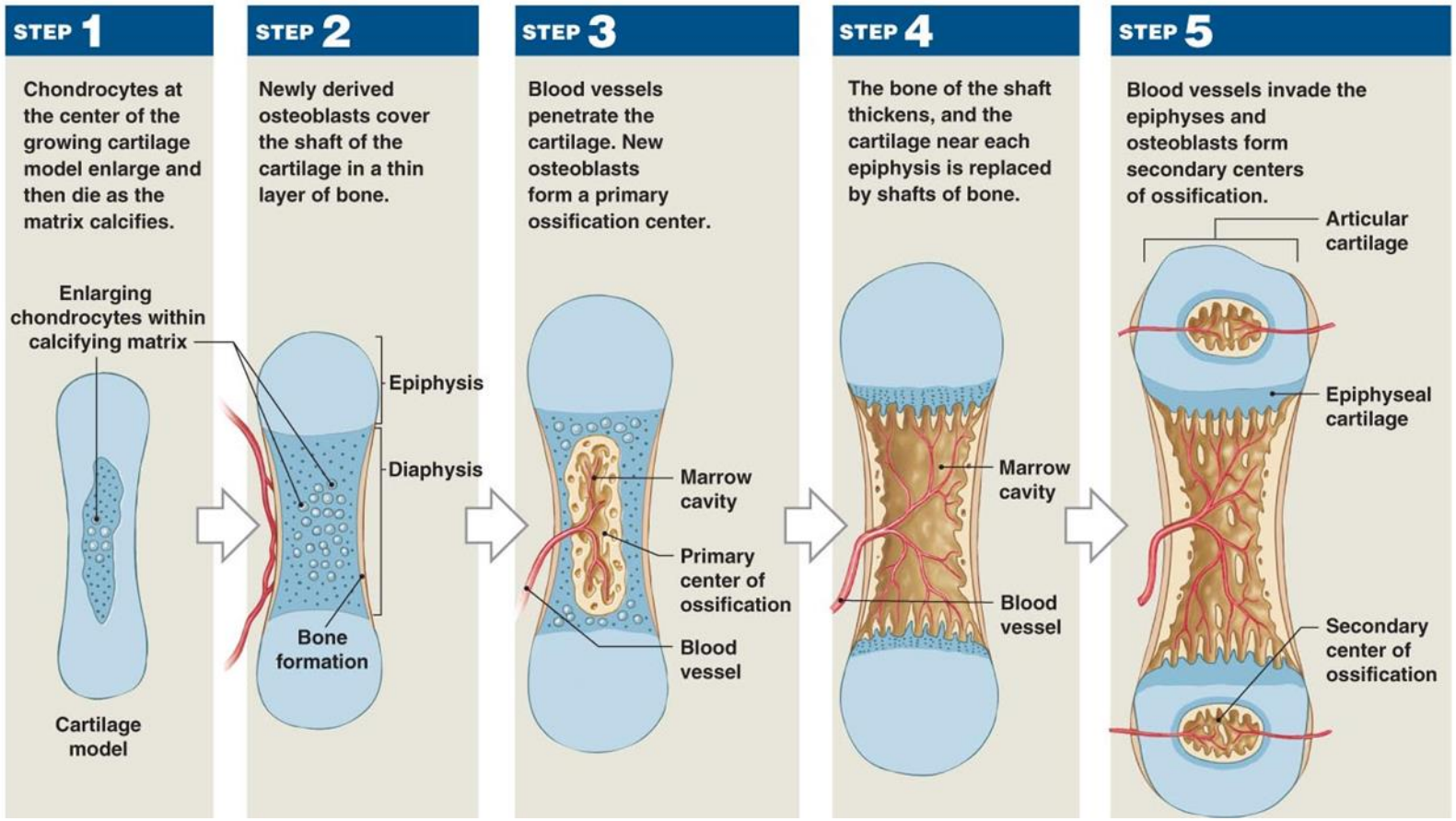

Figure 6 Bone Development Stages of the Fetus (Educatorpages, 2015)

As the fetus continues to develop in the womb, so does the skeletal structure. Once past week 9, cartilage rapidly forms the structure that will eventually form bones. In the last trimester of fetal development the bone begins to rapidly calcify and form a boney structure which pulls nutrients from the mother into the fetus. Following birth, all the bones have been formed but continue to grow with cells dividing rapidly forming larger calcified tissues Figure 7.

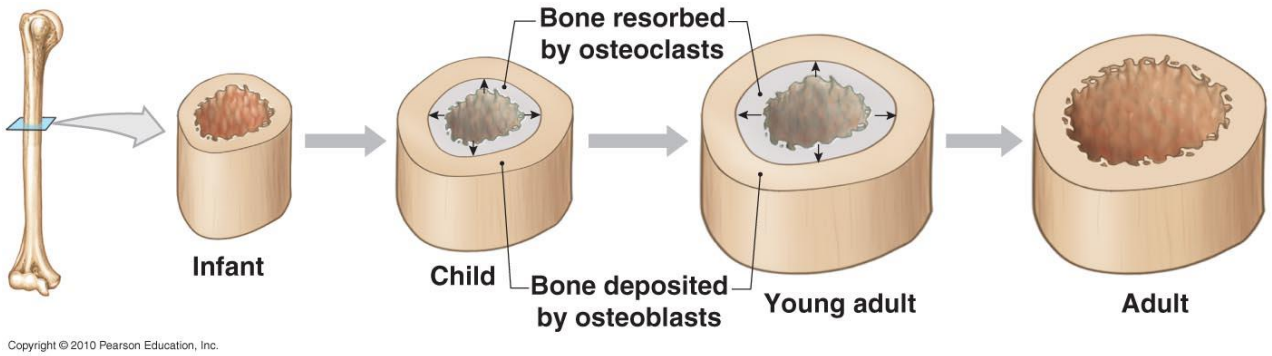

Figure 7 Apposition bone growth over time

The bones of an infant are soft and rapidly undergo bone resorption and growth. The process of bone resorption continues at a rapid pace until adulthood where bone development essentially ceases. In the case of rhesus macaques, peak bone mass density occurs at the age of 7 and 10 years for males and females respectively (Cerroni AM, 2000). The bone mass density then remains stable for females from the age of 10 to approximately 17 years, thereafter, there is a steady decline of bone mass density with advancing age (Turnquist JE, 2011). Osteoporosis is not prevalent in male nonhuman primates until the age of 19 at which time a significant portion of the life of the subject is over and is not considered a significant contributing factor to bone loss. However, during

the span in which peak bone mass density of bone apparently obeys Wolff's Law. Wolff's Law states: bone grows or remodels in response to the force or stress placed on it; appositional growth (growth in diameter) is controlled by the amount of mechanical stress and gravity placed on the bone: heavy usage leads to heavy bones and lack of use leads to atrophy (bone loss). In the event bone remodeling does take place, it takes place over a long period of time weeks to months, which slowly can build in defects or release defects form the calcium apatite. Figure 8 illustrates the bone resorption process by which stressed or fractured bone may undergo the remodeling process. In the bone resorption process osteoclasts break down bone, calcium (or strontium) is taken from bone and place into the blood stream, amid lysosomes stimulate the mobility of both Ca and PO_4 which are eventually released into the blood stream. Bone reformation t occurs when bone is injured or added strength is required. Osteoblasts move Ca^{2+} ions into the bone and mineralization occurs as it would in the developmental process (Teitelbaum SL, 2000).

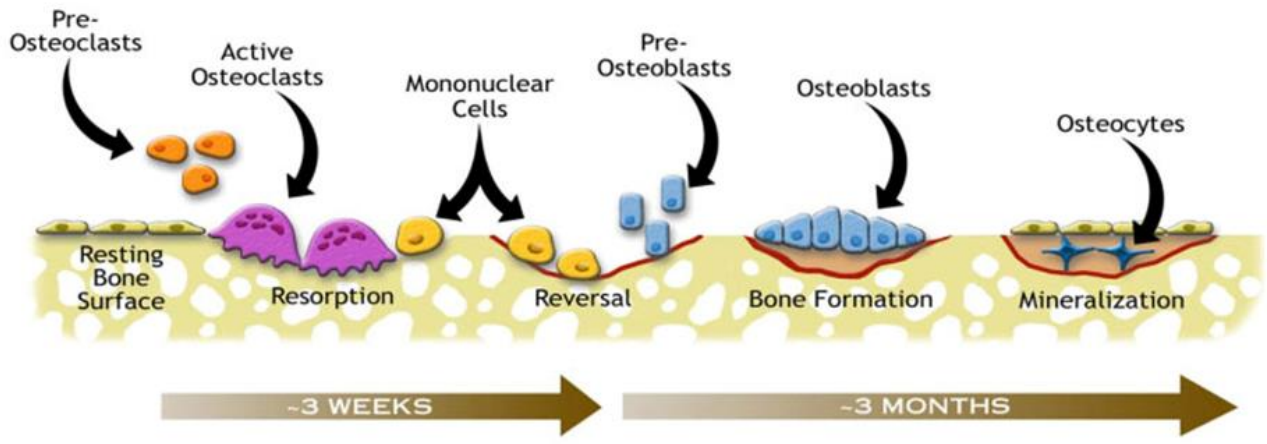

Figure 8 Bone Remodeling Cycle (University of Michigan, 2005)

2.3 Strontium Biology

The distribution of absorbed strontium in the human body is similar to that of calcium, with approximately 99% of the total body burden ultimately being found in the skeleton (ICRP, 1993). Pathways to absorption include: ingestion, inhalation, and absorption through the skin via direct absorption or through a superficial wound. According to studies of non-radioactive strontium, humans absorb some 11 to 30% of the strontium ingested into the skeletal structure (WHO, 2010). An age dependent absorption rate has been presented by which younger rats had a higher absorption at different ages (Taylor D, 1962). This was experienced mainly by an increased gastrointestinal absorption rate; although, age dependent gastrointestinal absorption into the body through the ingestion pathway has not been observed in humans. The inhalation pathway is more complex and depends mainly on the chemical species, and particle size of the strontium. The chemical form and size in which strontium particles are usually found has been used to determine its solubility class: days, weeks, or years (D, W, Y) (F, M, S), which in turn helps one to determine how long it takes the strontium to be absorbed into the body. A competing pulmonary clearance process to absorption is the phagocytosis of foreign particles by alveolar macrophages and their subsequent removal either up the ciliary escalator or by entrance into the lymphatic system (Cember H, 2009). The dermal absorption of strontium is known to be slow and through direct means. Wound absorption appears to be dependent on the physical aspects of the wound itself and the chemical species of the strontium (NCRP, 2006).

Strontium, once in the body, can act as an imperfect surrogate for calcium; the distribution of absorbed strontium mimics that of calcium, and strontium can exchange with calcium in the bone (ATSDR, 2004). Strontium distributes relatively uniformly within the bone volume, where it exchanges with calcium hydroxyapatite. The strontium to calcium concentration ratio in bone increases with age from $3x10^{-4}$ at birth to $5x10^{-4}$ in adults (Tanaka G, 1981). This ratio is shown to be approximately 10 to 20% higher in cortical bone than trabecular bone (Harrison GE, 1967). The main difference in the different classifications of bone, is that long bone tend to be under stress more than bone heads and thus increasing the remodeling rate. This increased resorption rate in turn allows strontium, which was bound in the bone matrix, to be released back into the blood stream.

Once the initial unabsorbed strontium exits the body through excretion, the only means of clearance is the exchange of strontium from the bone to the blood and then through urinary excretion. As strontium exchanges with calcium in the blood, it can be circulated throughout the biokinetic system and be excreted or reabsorbed by the bone. The long term elimination of strontium (i.e. the biological half time) from humans in the Techa River area was reported to be 28 and 16 years for males and females, respectively. The difference in these elimination rates was mainly due to a pronounced increase bone resorption rate in females after menopause (Tolstykh EI, 2011). These estimates of the long term elimination from the body reflect primarily the storage of strontium in bone and its slow recirculation back into the blood.

While examining short periods after exposure, elimination rates appear to be faster, this is thought to be due to soft tissue elimination. Other contributors to this route

can be attributed to the rapidly exchangeable bone volume. Considering the rapidly exchangeable bone volume, it appears that strontium follows the calcium pathway, it is either taken up rapidly by new bone formation or phagocytized in the extracellular fluid and excreted (Fraser R, 1960). After exposure to strontium ceases, the bone strontium content rapidly decreases in monkeys (Dahl SG, 2001). The relatively high clearance rate of strontium from bone can be explained by mechanisms of its incorporation. Strontium is mainly incorporated by exchange onto the crystal calcified surface unless bone is undergoing remodeling and in turn can be sequestered for long periods of time. As a result, radiostrontium is considered very detrimental to young adults who are still undergoing bone development. This increase in risk is reflected in ICRP guidance documents that restrict exposure in developing individuals. This can be observed in statements of strontium radiosensitivity that reflect decreases in individual's sensitivity with increasing age.

2.4 Internal Dosimetry of ^{90}Sr

Determination of the radiation dose and related health risks due to an internal uptake is a complicated task. Knowledge of the number of transformations and energy per transformation is essential to determining the absorbed energy in the target tissues. Once the absorbed energy is known it can be related to the health detriment of the individual. This type of information is valuable for medical, regulatory, and public health purposes. Assessing dose from an internal exposure is much more complex than that of the external exposure (J & P, 2008). Efforts have been made through the IDEAS project which was developed as a set of general guidelines for the assessment of intakes and internal doses from individual monitoring data, and to create a well-defined procedure for

assessing internal dose. Although, there still remains some shortfall because the plans outlined assume that the assessor has the use of sophisticated bioassay interpretation software (Doerfel H A. A.-S., 2007). Other major shortfalls are the number of assumptions that can be made that may change the end result of the internal dose calculation. Some examples of these assumptions are: assuming light work over heavy work, choice of solubility class, chemical form of radionuclide, and intake pathways to be taken into consideration to name a few. Taking all of the information into account, it is recommended in the IDEAS project to consult other knowledgeable experts in the field if the fit to data does not meet specific criteria.

As recommended by ICRP publications, the first step in assessing internal dose once measurement data is available is to evaluate the distribution and retention of a radionuclide in the body and organs through the use of biokinetic models (ICRP 1993 DOE-STD-1121-98, Section 7,). Essential to all calculations of dose for long-lived radionuclides like ^{90}Sr deposited in tissue is knowledge of the kinetics of retention; because the rate of elimination frequently has much more influence on dose than does the physical half-life. Using these kinetic models; the total number of disintegrations occurring in each source organ or tissue can be calculated. A dosimetric model is used to calculate the mean absorbed dose, D_T, to target organs; a result of radioactive decay, and the associated decay energies from each source organ. The type of radiation is taken into account by applying the radiation weighting factor (W_R) and hence this value correlates to the detrimental stochastic health effects. The equivalent dose in the tissue or organ (T) due to a given radiation type (R) is represented by the following:

$$H_{T,R} = W_R * D_{T,R} \qquad \textbf{(2.1)}$$

The total equivalent dose, H_T to an organ or tissue is therefore represented by the sum over R of all radiation types $H_{T,R}$:

$$H_T = \sum_R H_{T,R} \qquad \textbf{(2.2)}$$

The application of the tissue weighting factor (W_T) accounts for the contribution of harm done to individual organs and tissues to the overall risk of deleterious effects, which is the typical end point of dose assessment. The effective dose (E) then may be calculated in the tissue or organ (T) by the following expression.

$$E(Sv) = \sum_T W_T * H_T \qquad \textbf{(2.3)}$$

2.5 Systemic Biokinetic Models for Alkaline Earth Elements "Sr"

As has been discussed, strontium is a chemical and physiological analogue of calcium but has different biokinetics from calcium. Biological hydroxyapatite crystals of the bone discriminate between these elements. These biokinetics have been studied in human subjects and laboratory animals. The studies clarify the behavior of strontium at early times after intake but are considered by many to be lacking in long term information. The structure of the model for systemic strontium is similar to that of other calcium chemical congeners as seen in Figure 9. Simplifications include eliminating the effect of the transfer of strontium between the blood and blood plasma which is a simplified model for bone-volume seekers. Soft tissues are all grouped into three "other-tissue" compartments: ST0, ST1, and ST2; corresponding to rapid, intermediate, and slow exchange of activity with blood respectively.

The exchange mechanism between these components is the blood compartment. The blood is treated as a uniformly mixed pool that exchanges activity with soft tissues and the bone surfaces. The divisions of the soft tissues are classified by their three respective transfer rates with the blood. The liver and kidney are lumped into the model in these compartments and are not treated as exclusive compartments for strontium. The bone is divided into two types; cortical and trabecular bone, and further subdivided into bone surfaces and bone volumes. The bone volume is viewed as consisting of two pools; one that exchanges with activity in bone surface for a period of weeks or months, and a second, non-exchangeable pool by which activity is removed solely by the bone restructuring process or fractures. Activity depositing in the skeleton is assigned to bone surfaces; over a period of days a portion of the activity on bone surfaces moves to exchangeable bone-volume while the remainder returns to the blood plasma. Activity leaves the exchangeable bone-volume over a period of months, with part of the activity moving to bone surfaces and the rest to non-exchangeable bone-volume. The rate of removal from non-exchangeable bone volume is assumed to be the rate of bone turnover, with different turnover rates applying to cortical and trabecular bone. The only means by which strontium is assumed to leave the body is by fecal and urinary excretion. The transfer rates for this model are represented by Table 1 and are in units of inverse days (d^{-1}).

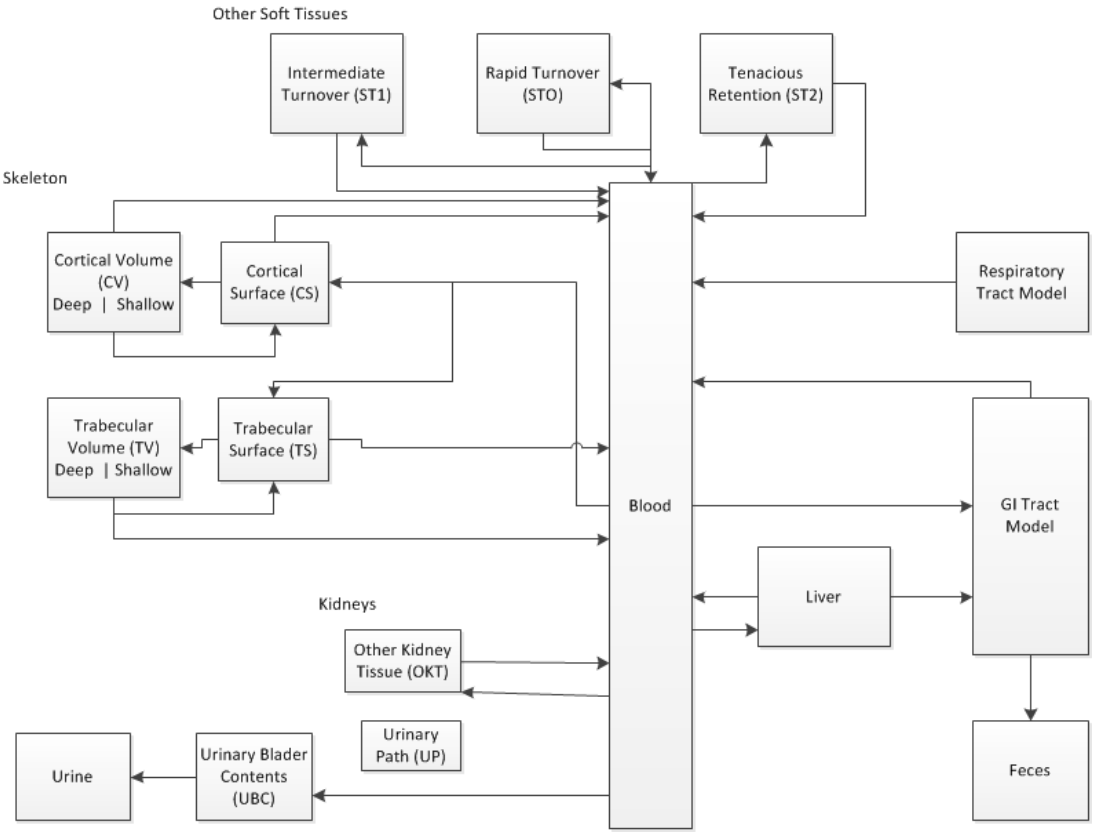

Figure 9 Strontium Biokinetic Model

Table 1. Biokinetic Transfer Parameters for ICRP-78 Model *(ICRP., Publication 67: Age-dependent dose to members of the public from intake of radionclides: part 2, ingestion dose coefficients, 1993)*

Starting Compartment	Ending Compartment	Default Transfer Rate (d^{-1})
BLOOD	ST0	7.50
BLOOD	ST1	1.50
BLOOD	ST2	$3.00\ 10^{-3}$
BLOOD	CORTICAL SURFACE	1.67
BLOOD	TRABECULAR SURFACE	2.08
BLOOD	RC CONTENTS	$1.16\ 10^{-1}$
BLOOD	URIN BLADDER CONT	$5.78\ 10^{-1}$
CORTICAL SURFACE	EXCH CORT VOL	$1.16\ 10^{-1}$
CORTICAL SURFACE	BLOOD	$5.78\ 10^{-1}$
NONEX CORT VOL	BLOOD	$8.21\ 10^{-5}$
EXCH CORT VOL	CORTICAL SURFACE	$4.30\ 10^{-3}$
EXCH CORT VOL	NONEX CORT VOL	$4.30\ 10^{-3}$
TRABECULAR SURF	EXCH TRAB VOL	$1.16\ 10^{-1}$
TRABECULAR SURF	BLOOD	$8.21\ 10^{-4}$
NONEX TRAB VOL	BLOOD	$4.93\ 10^{-4}$
EXCH TRAB VOL	TRABECULAR SURFACE	$4.30\ 10^{-3}$
EXCH TRAB VOL	NONEXCH TRAB VOL	$4.30\ 10^{-3}$
ST0	BLOOD	2.50
ST1	BLOOD	$1.16\ 10^{-1}$
ST2	BLOOD	$3.80\ 10^{-4}$
URIN BLADDER CONT	URINE	12.0

2.6 ICRP Systemic Model Development

The development of the systemic model for ^{90}Sr relies heavily on environmental exposure data to investigate physiological mechanisms (Loutit JF, 1967). The most recent data originated from the Techa River cohort which was exposed to strontium through pollution of the river. Other significant sources of environmental data contributing to the development of the model were derived from the fallout of nuclear weapons testing. The quality of the experimental data is reflected in the accuracy of the model. Also, the data used to validate the model is indicative of the quality of the model itself.

An interest in understanding ^{90}Sr biokinetics began in the 1950s after large scale atmospheric nuclear weapons tests were conducted; resulting in the dispersal of large quantities of strontium in the environment (US EPA, 2012). The data from the atmospheric testing and animal studies were used for the development of the ICRP strontium biokinetic model (Leggett, 1992). Strontium biokinetics from food, milk, and other contaminated items due to the fallout from the nuclear tests are complicated but give good general knowledge. Interpretation of this environmental data is further complicated by the fact that skeletal burdens were measured over an extended period and the ^{90}Sr intake function was not well established (Tolstykh, 2011). The studies do, however, provide substantial evidence that once ^{90}Sr is absorbed into the blood stream, it transfers to bone and accumulates there and resides for a long period of time (Synhaeve N, 2011).

There are many proposed alternative models describing the biokinetics of strontium and other nuclides (Hollrigl V, 2002). The problem with the proposed changes is that they are using the same dataset with which the original model was created. Albeit, some data sets represent human subjects but they were not experimentally controlled cases of uptake. This problem of circular logic apparently has not lead the ICRP to change the model. ICRP publication 67 models were assumed to provide a reasonable representation of the distribution and retention of strontium and radium in the body for all age groups. ICRP points out the large uncertainty of these models; noting that age and sex specific skeletal retention may deviate from the central model predictions. This deviation needs to be better understood to more precisely determine the difference in male and female cases.

2.7 Validation of ICRP Systemic ^{90}Sr Model

As part of the investigation of the ICRP biokinetic models for strontium, a review of reports on the available humans and animal biokinetic behavior and reviews of chemical congener data, or data collected from humans who accidentally ingested ^{90}Sr was undertaken. When mice drank water containing ^{90}Sr, it was observed that a vast majority of the long term assimilated ^{90}Sr was located in their bones, as predicted by the default strontium model (Synhaeve N, 2011). More recently acquired data show acceptable agreement with the ICRP 67 predictions for ^{90}Sr retention in skeleton, although some authors have suggested that the ICRP 67 model needs to account for both age and gender differences in strontium metabolism (Sagine NB, 2003). Other reports

also suggest that ^{90}Sr biokinetics are strongly dependent on both age and gender (Synhaeve N, 2011) (Leggett, 1992) (Sagine NB, 2003). The rate of ^{90}Sr elimination appears to be strongly dependent on the rate of bone regeneration, which was seen with advancing age during evaluation of the Techa River cohort (Tolstykh EI, 2011). During advancing age bone regeneration slowed and bone loss increased which decreased the overall strontium body burden and is directly related to the rate at which strontium is taken into the bone. Mouse studies demonstrate a significant difference in the activity residing in the skeleton based on age and sex. This study provided additional evidence that uptake of ^{90}Sr is reduced in adults compared to juveniles (Tolstykh EI, 2011). It has been thought that this observation is likely due to difference in bone remodeling rates and potentially osteoporosis.

It should be noted that many alterations and substitutions have been proposed to the ICRP biokinetic models (Tolstykh EI, 2011) (Tolstykh & Degteva MO, 1998) (Li BO Wei, 2006). Evaluating the Techa River cohort of human data, Sagine found that the ICRP model structure was adequate to describe ^{90}Sr retention in bone, but that the model could be improved upon (Sagine NB, 2003). Suggestions for improvement include the simplification of the biokinetic model by reducing the number of compartments and implementing a multi-exponential function to predict strontium retention or by the ability to write expressions to modify the exponentials as a function of time to account for things such as age and gender (Malinovsky G, 2013). One idea is to write switching equations of n variables that includes a function that assigns to each a binary sequence of length (n) which assigns the number 0 or 1 signifying that the equation is either active or inactive.

When used with other biokinetic equations, more complex parameters can be taken into account and a streamlined linked model for all humans can be derived.

2.8 Proposed Systemic Models for Male Nonhuman Primates

The International Commission on Radiation Protection (ICRP) adopted the current strontium model described in ICRP publication 78 (ICRP, 1997) based upon the skeletal distribution of fallout ^{90}Sr, and results of animal experiments (NCRP, 1991). The animal data mostly reflects short-term experiments that may inaccurately describe the long-term biokinetics of strontium. The current effort compares the prediction of the ICRP 78 strontium model with nonhuman primate (NHP) data accumulated for long periods of time (20 years plus) post injection. The study used NHP data to test the default ICRP transfer rates and kinetics. Subsequently, three simplified models A, B, & C (see Figure 1), were developed and tested on the composite NHP data and independent test cases. Transfer rates and kinetics were developed by fitting to the data such that the transfer rates reflect the activity residing in the skeleton and the intake for a composite male cohort. The three simplified models tested were based on a classic three-

compartment pharmacokinetic model of strontium in bone (Bonate, 2006), using data obtained from studies performed by Pat. W. Durbin and colleagues (Durbin P.W., 1993)[1].

Pharmacokinetic (PK) modeling is a systematic way to study the change in material distribution over time in the body. Concepts of physiologically based pharmacokinetic modeling were introduced decades ago. The initiation of the increased use of PK modeling to describe more detailed biokinetics of drugs in the USA and Europe may have also contributed to the wider use of this modeling technique, as PK models can bridge animal, adult, and pediatric pharmacology (Kahlil F. 2011; Himmelstein K.J. 1979). The development of such models involves five key steps: (1) specifying general model structure, (2) specifying key tissues, (3) developing model equations, (4) defining model parameterization, and (5) model evaluation.

Strontium, radium, and lead, all act as chemical congeners of calcium and can substitute into the calcium positions of the crystalline apatite in bone mineral (Vaughan J, 1981). Radiostrontium has often been used as a tracer for calcium in kinetic studies; although radiocalcium and radiostrontium behave differently in the mechanism by which they are incorporated into the bone; both have high bone affinities. Divergences in the kinetics of calcium and strontium can be seen in studies of their rate of excretion and rate of blood elimination. After intravenous injection; these two elements differ substantially in their rates of intestinal absorption, renal excretion, and accumulation into bone (Wasserman, 2012). One important difference is that the total amount of strontium in standard man is small compared to calcium, accounting for 0.00044% and 1.4% of body

[1] Dr. P.W. Durbin and colleagues were supported by the Director, Office of Energy Research, Office of Health and Environmental Research, of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

mass respectively. However, biological differences between the two elements exist, explicable in part by the larger size of the strontium atom (Nielsen, 2004). This size difference leads to the preferential transfer of calcium to the skeleton and throughout the remainder of the body.

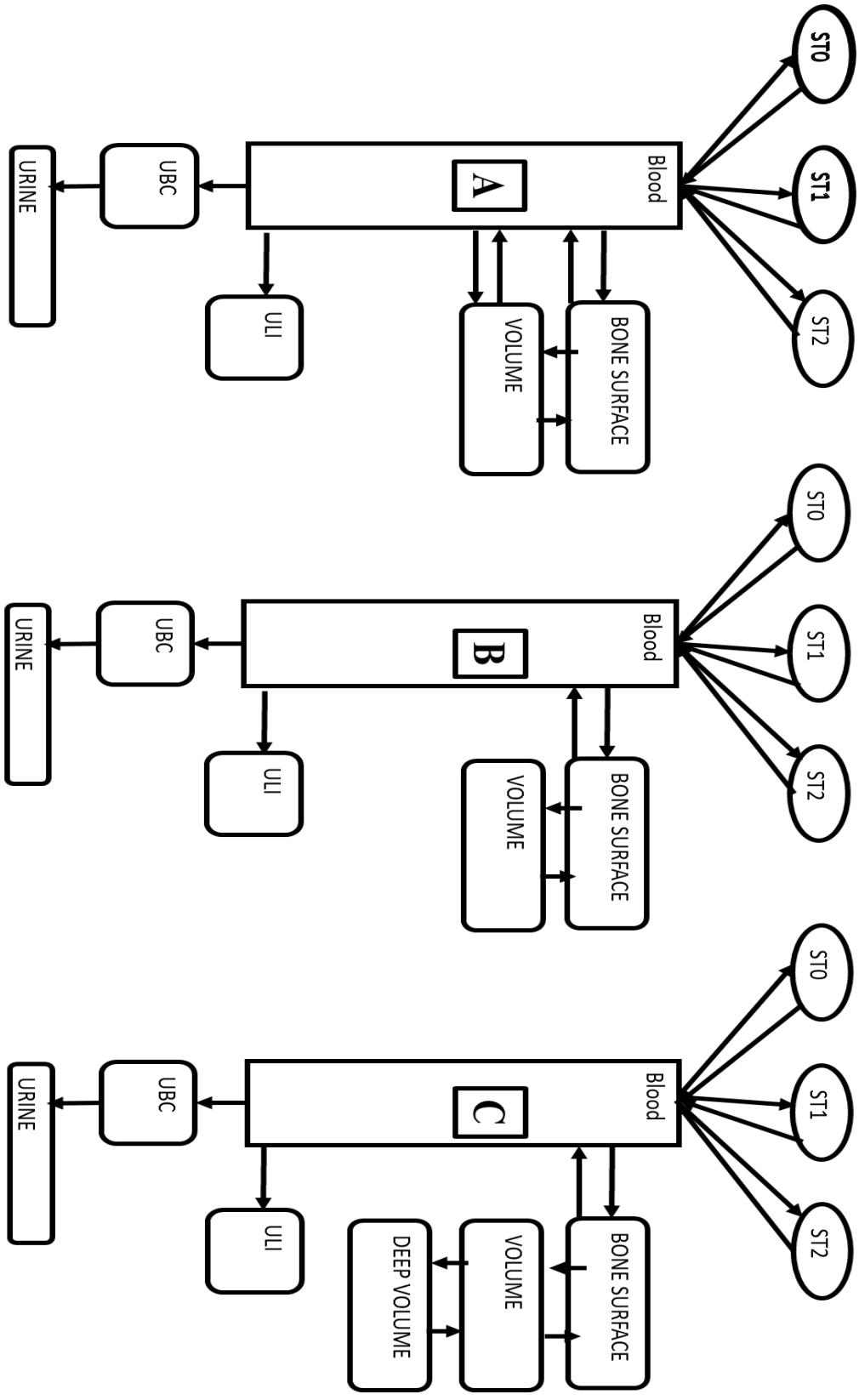

Figure 10 Model A, B, C Biokinetic Models

Model A, is a three-compartment model for bone that has been previously utilized for bone seeking imaging compounds, biophosphates, and other agents (Lin, 1996) (Canniggia A., 1980). The model structure in question considers bone to be made up of noncalcified tissues (Bone Surface) and calcified bone (Bone Volume). The flow between both the bone surface and the volume is representative of the osteoblast bone resorption process taking place, and ion exchange. In this continuous process the bone is dissolved releasing material into the blood which takes about 3 weeks. Subsequently, Parathyroid hormone is released into the blood stream and the chemical calcitonin calls for the body to produce collagen and bone matrix proteins. The presence of these proteins promotes the development of a collagen framework which may entrap strontium. Strontium may also substitute in the calcium positions during calcification. Strontium can then be built back into the bone and calcified as new bone is developed. The direct interaction of the bone volume with the transfer compartment is suggested to be representative of blood traveling through and interacting with small micro fractures or cancellous bone (Barrere F., 2006). Model B is similar to model A, but without the interaction of the blood within the bone volume. The third model, model C, is a four-compartment model that is similar to those proposed for biophosphates; a bone seeking agent (Porras AG., 1999). Strontium, similar to biophosphates, has an affinity for bone and is not readily transported through the body after bone deposition. The four compartments that make up bone transfer in this model (Model C) include the blood, noncalcified tissue, remodeling bone, and inactive bone all acting in a linear chain. It is thought that the noncalcified tissue or bone fluid acts as a barrier between transfer of material to and from the bone and the transfer compartment because of its ability to discriminate against strontium prior to

the calcification process (Ogata K. 1979; Triffitt JT. 1969). Once the strontium has been incorporated in the bone, it is only available for resorption in the bone fluid during the bone remodeling process. Once the skeleton has become fully mineralized in adulthood, a large portion of the skeleton is thought to be unreactive (Leggett R.W., 1982). This unreactive skeleton fraction is the basis for the deep volume, or inactive bone, which would act as a nearly permanent reservoir for material in the bone.

2.9 Female Nonhuman Primate Systemic Model and Placental Transfer to Off-Spring

The reproductive and skeletal system of human and other old world anthropoid primates are similar, making female nonhuman anthropoids a good animal model for research. The remolding of the female skeleton system can be observed to be more complex than that of the male skeleton. One main reason for this complexity is the difference in age for the male and female to reach a peak bone mass density (BMD); 7 and 10 years respectively for rhesus monkeys. Humans males in contrast, have a higher bone mass density in comparison to the female **(Cerroni AM, 2000)**. The BMD in NHPs remain stable for females from the age of 10 through 17 years, thereafter, there is a steady decline of BMD with advancing age **(Turnquist JE, 2011)**. This process is not prevalent in the male cohort until 19 years of age, at which time they have lived a significant portion of their lifespan. Remember, females of both humans and NHPs tend to live longer and may suffer the effects of osteoporosis longer. The effects of osteoporosis on the retention of radiostrontium in the bone is similar to that of calcium. When calcium in the bone undergoes resorption, it allows strontium to be released from

the intracellular calcium binding sites. If the resorption process is not balanced with enough new bone deposition, it will continue to reduce the sequestered strontium and calcium over time; in turn reducing the long term retention in females in comparison to males. The difference in bone retention is the reason different biokinetic parameters should be used for the female when compared to its male counterpart. The different model parameters of the optimized model C from Krage et al. were used to investigate the need for modified transfer rates and compare against the ICRP 78 systemic model.

The female skeleton has been endowed with specific mechanisms that balance the requirements of the developing fetus and neonate for calcium and strontium with the mother's need to maintain homeostasis. The affinity for homeostasis during fetal development leads to the decorporation of calcium and strontium in the mother which is subsequently transferred to the fetus. The complex transfer of strontium has been shown to vary based on the time of intake by the mother with respect to the date of conception of the fetus (ICRP, Publication 88 Doses to the Embryo and Fetus from Intake of Radionuclides by the Mother, 2002). This strontium model originally developed by Fell calculates a ratio of mother's whole-body concentration ratio at term to that of the fetus (Fell TP H. J., 1998). The transfer rates of strontium from the mother were developed by analyzing the weapons-test fallout of ^{90}Sr. The ratios of ^{90}Sr relative to calcium concentrations was determined in the diet of the female and in the ratio of strontium to calcium in the fetal bone. The analysis showed that the ratio in fetal bone to be from 0.05 to 0.15 the ratio found in the diet.

The distributions between the fetus and mother predicted by models have been generally consistent and well-understood for intake during pregnancy **(Holmberg B.,**

1960) (Nelson A, 1965). However, there have been some discrepancies with the fetus to mother whole-body concentrations at term for an intake prior to conception. Originally the literature showed a concentration of fetus at birth to mother (CF:CM) of 0.1 for an intake by the mother 52 weeks prior to conception as shown in Table 2 (Fell TP, 1998). This value was later modified to have a CF:CM ratio of 0.2 at 26 weeks prior to conception which was then adopted by ICRP in report 88 **(Fell TP J. H., 2001) (ICRP`, 2002)** Evaluation of ^{90}Sr concentration in six still born human fetuses and their mothers was conducted based on data from the human bones of inhabitants of the Techa river region (E.I. Tolstykh, 1998). Tolsytykh et al. observed CF:CM values ranging from 0.01 to 0.24 for intakes many years prior to conception. Various animal studies and this evaluation demonstrate agreement with the ICRP transfer ratios **(A. Nelson, 1965) (J.W. Stather, 1987)**. The transfer of radionuclides to the fetus is of increased concern because the sensitivity of the fetus is greater than that of an adult. Considering the case of bone seeking radiostrontium, this is of particular concern because strontium once incorporate into the bone matrix may never undergo a resorption process during the subject's lifespan **(ICRP., Publication 20: Alkaline Earth Metabolism in Adult Man, 1972)**.

Table 2 Placental Transfer Rates

Fetus:Mother whole-body concentration ratios at term for intakes of Sr either prior to conception or during pregnancy.					
Fell (1998)		Fell (2001)		ICRP-88	
Time of Intake (Weeks)	CF:CM	Time of Intake (Weeks)	CF:CM	Time of Intake (Weeks)	CF:CM
-52	0.1	-26	0.2	-26	0.2
8	0.5	0	0.3	0	0.3
12	1	10	0.7	10	0.7
24	3	15	2	15	2
30	6	25	4	25	4
36	9	35	8	35	8
8-36 Chronic	5	0-38 Chronic	4	0-38 Chronic	4

2.10 Ingested Radioactive Strontium-90

Everyone is exposed to small amount of strontium-90, since it is widely dispersed in the environment and the food chain and has been since the 1940's weapons testing. Dietary intake of ^{90}Sr, however, has generally fallen since the cessation of nuclear weapons testing due to natural weathering and radioactive decay. The most notable ingestion exposure occurred through the contamination of the Techa River from 1949 to 1956. The population cohort affected consisted of approximately 30,000 individuals (EI Tolstykh, 2011).

The gastrointestinal absorption of strontium largely depends on age and may vary from 90% of the elements dietary intake in infants to 10% in the elderly (EJ, 1977). Several mechanisms for strontium transport through the intestinal wall have been

postulated (Cabrera WE, 1999). Some authors suggested that in contrast to calcium, strontium is absorbed entirely via passive diffusion, i.e., paracellular transport (Dumont PA, 1960) (Karbach U, 1987). However, some have proposed two routes of entry for strontium into the transfer compartment: carrier-mediated and diffusion-mediated (Papworth DG, 1970). With the exception of infants, it can generally be stated that strontium is absorbed to a lower extent than calcium, the strontium/calcium absorption ratio being ~0.50 (Milsom S, 1987). However, the intestinal absorption of strontium can increase under fasting conditions and is negatively affected by a high dietary content of calcium, phosphate, or chelating agents such as sodium alginates (Kostial K, 1967) (Kositial K B. S., 1965), which are of substantial interest in view of their ability to inhibit the intestinal absorption of the element in animals and man without affecting calcium absorption (Patric G, 1967) (Moore W, 1965). Experimental studies have further demonstrated that intestinal strontium absorption is gradually increased during pregnancy and lactation, with a maximal fraction of absorption at the end of the lactation period (Kositial K G. N., 1972).

When determining the internal ingestion of ^{90}Sr by nonhuman primates (NHP) from bioassay measurements, the behavior of these radioisotopes must be known, especially in relation to the systemic transport through the body. Investigations of the biokinetics of radiostrontium in humans and nonhuman primates have been made and have received some recent attention (NB Shagina E. T., 2015). Models proposed by Krage et al. for nonhuman primate males and females, have focused on a simplified ICRP-78 type systemic model for strontium. The Krage model is simplified to a three compartment bone model instead of a six compartment model suggested by ICRP.

Current work in strontium internal dosimetry has been focused on developing more representative models to specific nuclides and populations of concern; mainly females and their offspring (N.B. Shagina, 2015). However, most of these studies were not conducted in a laboratory setting with known input parameters and were mainly concerned with humans except for a few studies on nonhuman primates.

Another purpose of the present study was to investigate the relation between strontium-90 transfer rate from the G.I. tract to blood and also determine the fraction of the radioisotope being retained in the skeleton in the long term. The current work uses a female NHP systemic strontium model developed by Krage et al. paired with the International Commission on Radiological Protection (ICRP) Publication 30 gastrointestinal tract model (Krage) (ICRP, Limits for Intakes of Radionuclides by Workers Publication 30, 1982).

Chapter 3 DATA COLLECTION AND MEASUREMENTS

3.1 Laboratory Experiment Outline

Between 1958 and 1982, a series of studies were conducted at the Division of Research Medicine and Radiation Biophysics in affiliation with Lawrence Berkley Laboratory. The studies were conducted to obtain ^{90}Sr biological data as a basis to improve human biokinetic models. Previous animal studies mainly focused on rats. The lifespan of rats was postulated to be too short for a complete understanding of what might occur in humans, especially for long lived bone-seeking radionuclides like ^{90}Sr (Durbin P.W, 1993a). Pilot studies suggest that biokinetic data collected from macaque monkeys would serve as an acceptable surrogate for the development of a human biokinetic model for bone seeking radionuclides (Durbin P.W, 1993a).

Using monkeys as research subjects has a unique history within the topic of animals in science. As the animals most closely related to humans, phylogenetically, physiologically, and anatomically; they have important uses in research (IPS, 1995-2014). The use of primates in biomedical research has led to numerous medical advances and an understanding of biokinetic modeling with radionuclide translocations. Although primates are available for research, there are pressures not to use them, including the high cost of maintenance of a program and in some cases their endangered status in the wild. Their close genetic relationship to humans, which makes them the appropriate surrogate for human health research, also gives rise to ethical concerns (Rodgers J, 2015). The U. S. Federal government owns or supports approximately twenty-three thousand monkeys for research. (NIH, 2014).

Approximately 80 monkeys were exposed to ^{90}Sr in the Durbin study. The study included exposure by four modes: intravenous injection, intramuscular injection, intraperitoneal, and a feeding regime. For the groups of males and females which injected with ^{90}Sr, a one-time injection was prepared with the desired activity diluted from a concentrated stock solution. The stock solution was prepared by diluting 3.7 $MBq\text{-}ml^{-1}$ in 2N HCl and stored in a refrigerator. The required injection volume was diluted in sodium citrate (30 $mg\text{-}ml^{-1}$) in a serum bottle. The desired volume for each monkey (1 to 5ml) was drawn into a glass syringe; after 1967, syringes were weighed filled and empty for a more accurate measurement of the amount delivered. An additional syringe containing a measured volume (or mass) of each solution prepared for injections was expressed into a volumetric flask containing 2N HNO_3 to provide counting standards for a monkey injected on a particular day. The quantity of ^{90}Sr injected into each monkey was inferred from three separate calibrations of these counting standards: (i) measurement of total beta activity with a calibrated thin-window GM counter, (ii) measurement of separated ^{90}Y daughter by an outside contractor, (iii) measurements of bremsstrahlung with a pair of calibrated thin NaI(Tl) crystals (Durbin PW, 1993b). The intravenous (i.v.) injections were made into superficial veins of the calf and ankle, while intramuscular injections were made into the thickest part of the thigh.

Subjects which were orally administered strontium were separated in independent high level “hot” cages during the entirety of the feeding and three weeks after the concluding oral administration of ^{90}Sr. The feeding consisted of five or ten equal daily fractions; by administering 20 to 30 µL of concentrated ^{90}Sr citrate solution which was administered into a small piece of fruit. The total activity administered to the subjects

was 500 MBq or 1,000 MBq of material which was selected independently of any known factors. The subjects in the feeding regimen had there excreta collected in a stainless steel pan at the bottom of the cage. The sole purpose of collecting excreta was to minimize the contamination of monkey fur and to assure the safe waste disposal and no attempts were made for analyzing the excreta. It is important to note that no correction or analysis was conducted to determine the activity that was fully ingested by the subjects.

3.2 Excretion Collection

The excreta from the subjects were collected from all monkeys daily or every other day for the first two weeks after the ^{90}Sr injection. During that time, urine and feces were collected separately. This occurred except for a few monkeys early in the study where these materials were not separated. After the initial two weeks, samples were collected twice a week for six to twelve months. Subsequently two week time intervals of collection were combined 4 to 6 times a year until sacrifice. The main reason for the feces collection and analysis was to provide information necessary for the disposal of the biological material, hence not all excreta was radiologically analyzed.

3.3 Blood Sampling Procedures

Blood samples for the subjects were drawn from superficial leg veins at various frequencies. Frequent early blood samples were taken from some animals in the study to help define the kinetic pattern of clearance. When obtaining more frequent blood

samples, small aliquots of blood (1 to 3 ml to minimize blood loss) were drawn several times in the first 6 to 8 hours, twice daily for 3 or 4 days, once daily for about two weeks, and at succeedingly longer intervals thereafter. Blood was drawn from every animal in the colony at least twice a year for hematological examination. When blood was drawn at the less frequent intervals, approximately 3 to 10 ml of sample volume was obtained depending on the subjects mass. The blood was collected in syringes that were pre-weighed and post-weighed after dispensing in order to obtain the sample weight.

3.4 Whole-body Counting

During the investigation, *in vivo* measurements of strontium retention (whole-body counts) were conducted at regular intervals. The whole-body counts were initiated half-way through the study once a whole-body counting system was made available, so there is a lack of data early on for some of the subjects. Once the whole-body counting study was initiated, monkeys were tested at minimum bi-annually. Additionally, if monkeys had to be tranquilized for other reasons, they were also whole-body counted.

Concurrently with every whole-body counting procedure, the animals were tranquilized and weighed. The monkey was then placed into a carrying box in a curled up position as shown in Figure 10 and held in place by packaging material Figure 11. The reason for the packing in the tube was to generate a similar geometry for each subject tested. The whole-body counter system, consisted of a shielded steel chamber or "cave" designed by. L.W. Tuttle for whole-body counting of monkeys (Goksel, 1961). The facility used for the counting setup was a low background room. The room was setup to

allow for the precise position of the detector with respect to the counting subject. The cage was positioned such that the central point of the box-lid was directly below the mid-point of the crystal face shown in Figure 12. This position allowed for maximum counting efficiency as verified with a counting standard designed from another monkey case. The radiation detector used was a 4-inch diameter by 2-inch thickness thallium activated NaI crystal. The detector was calibrated to detect the external and internal bremsstrahlung from pure beta emitting radionuclides (GE Harrison 1955; K Liden 1955; N Starfelt 1955). The calibrations standards used consisted of phantoms designed to represent the NHP's mass, shape, and density. To account for the natural fluctuation of the background, a non-radioactive monkey was used for background subtraction to quantify the known amount retained in the body (Goksel, 1961).

Figure 11 Whole-body counting position

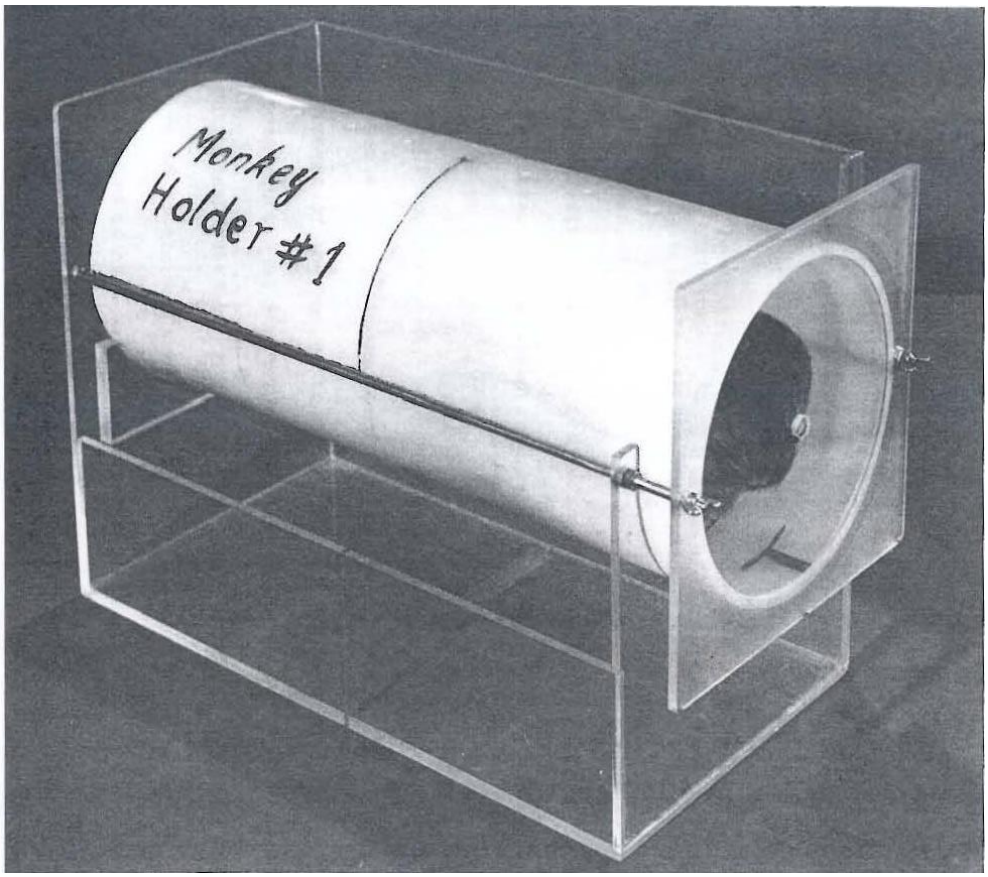

Figure 12 Whole-body Counting Setup

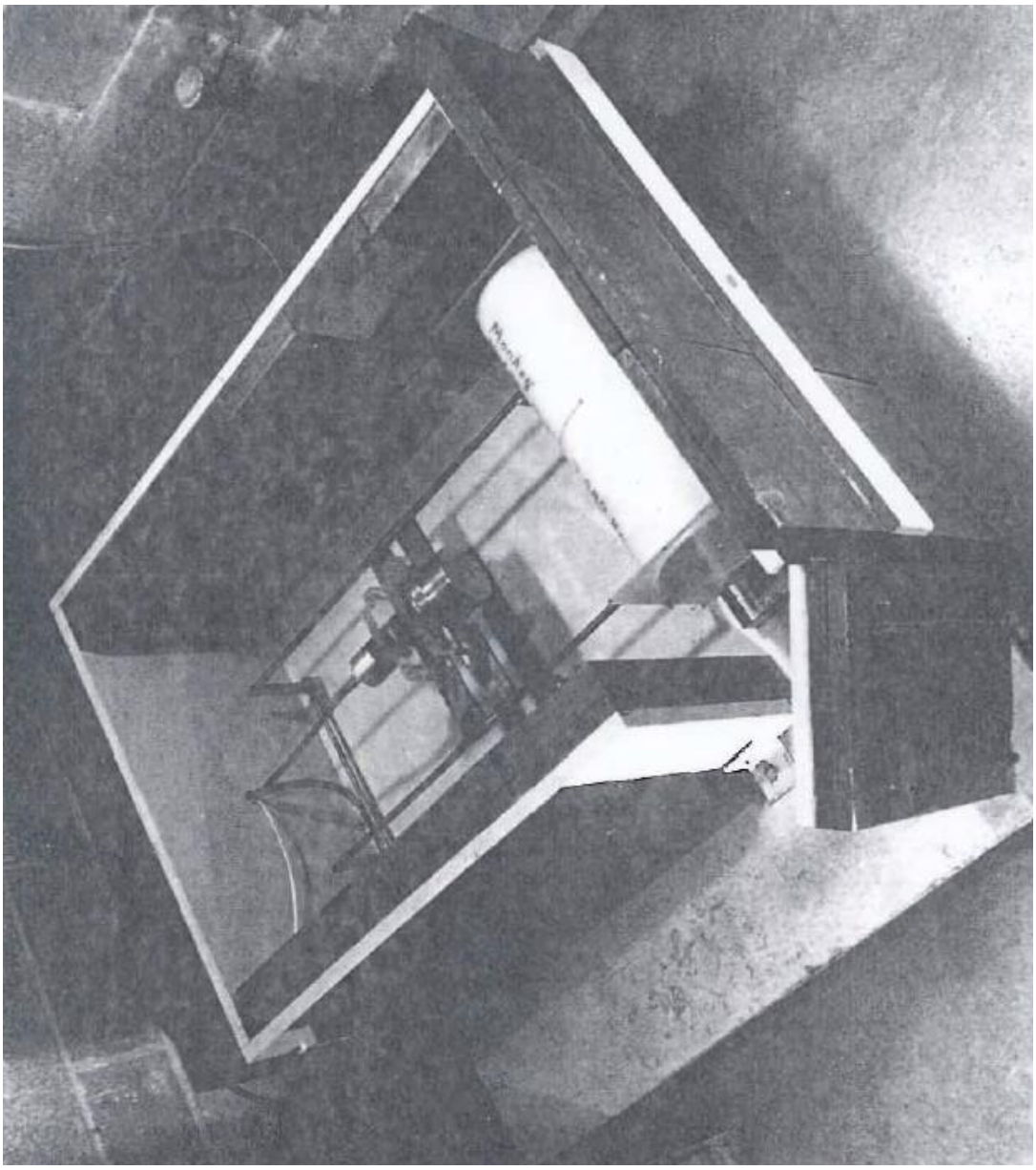

Figure 13 Whole-body Counting Chamber

3.5 Necropsy Procedures

The subjects were sacrificed for further analysis if they became ill or at the preplanned time. This was done with an overdose of sedative from 1 to 5,700-days post injection. Following the sacrifice of animal, a necropsy was performed. During the

necropsy, the thoracic organs and abdominal organs were removed. The blood pool remaining was removed to the extent feasible. The blood pool was extracted from the inferior vena cave via a catheter. The excess fecal matter was removed from the gastrointestinal tract and added to the final fecal collection. The soft tissue was separated from the skeleton and both tissue types were weighed before being and dried in an oven at 100 ^{o}C. The bones were disarticulated and any remaining flesh or cartilage removed. The leg in which the injection took place was analyzed separately as a whole prior to this process. The bones after disarticulation were then further subdivided into multiple segments and radioanalyzed.

3.6 Sample Preparation Techniques

After oven drying: blood, bone, excreta, and tissue; samples were heated in a furnace at 500 to 600 ^{o}C until they were reduced to ash. The total ashed weights of the bones were recorded. Dry-ashed excreta and large soft tissues were digested with concentrated HNO_3, and 30% H_2O_2 to eventually form a carbon free salt. The small ashed samples were further processed by dissolving them in 6N HNO_3 and then they were evaporated onto glass or steel planchets. The larger samples were acidified for a longer period of time to fully digest the salts. The acid in the samples were neutralized by the addition of NH_4OH, evaporated, and ultimately cooled and weighed.

During analysis of the individual excretion samples, it eventually became inevitable that the activity in the individual samples would be below detection capability. The lower activity in the samples was due to the time post injection of ^{90}Sr and the

limited initial injected activity (Durbin, 1993). This problem lead to longer collection periods for excreta. Collection periods were increased to one or two weeks at 6 to 12 months post-injection.

3.7 Bio-Assay Sample Counting

The bioassay samples collected were analyzed by different detection systems throughout the study as better technology was introduced. The detection system as the study started was an in house built GM tube which had a detection efficiency of 37% for a thin film and dropped to 21. 5% for the more massive ashed samples. The three commercial systems used were:

i. Nuclear-Chicago gas flow proportional counter

ii. Nuclear-Chicago 5-cm thick NaI(Tl) detector

iii. Dual NaI (Tl) crystal set up for counting ^{90}Sr / ^{90}Y decay products (Durbin 1993). Over time, components of the counting system were upgraded and replaced, but due to the high quality control the replaced parts did not degrade analysis results.

The skeleton of the subjects to undergo analysis were disarticulated and soft tissue removed. The segments were then weighed wet and again after they were ashed for counting. Some soft tissues, fecal, and urine samples after oven drying and dry ashing, needed additional wet digestion with concentrated acid and hydrogen peroxide. These samples were dissolved in 6N HNO_3 to generate fully dissolved homogeneous mixtures. The mixtures were then either prepped for counting in 14-ml test-tubes and counted using a well scintillator, or plated out onto planchets for counting.

To correct for due to self-absorption of the samples, self-absorption correction curves relating the percent transmission of ^{90}Sr / ^{90}Y to dry mass on the planchet were prepared. The curves were prepared using dissolved bone ash or reagent grade $Ca_3(PO)_2$. The self-absorption curve for ^{90}Sr / ^{90}Y in excreta samples was prepared using excreta ash in order to compensate for the presence of the small mass of non-volatile insoluble residue containing little or no radioactivity. The plant diet the monkey was on contributed to a small, but detectable, amount of ^{40}K, which increased the background beta count rate in urine and combined excreta samples. Over the range of dry samples weights of 20 mg to 200 mg on the planchets, ^{40}K accounted (on the average) for 0.045 to 0.085 counts/min/mg, uncovered or covered with a 64 mg cm^{-2} aluminum filter, respectively. Accounting for these types of error in the activity provided more reliable and robust data to analyze.

Chapter 4 ANALYSIS METHODS

4.1 Using Bioassay Data to Estimate Intake

Bioassay samples and *in vivo* measurements are undertaken to quantify the intake after a potential uptake of radioactive material. The measurement of the radioactivity in the body's organs or in the whole-body (in vivo), or measurements in samples of excretion (in vitro), must be interpreted using biokinetic models to quantify the radioactive material taken in to the body. These mathematical biokinetic models describe the translocation, distribution, and elimination of specific radionuclides in specified physical and chemical forms. Most biokinetic models attempt to describe activity in organs and excreta as a function of time following intake, from which a committed effective dose can be calculated using the product of the intake and dose coefficient (Doerfel H A. B., 2006).

An overview of the analytical treatment of models for internal dosimetry is present in Publication 30 (ICRP 1978). However, the method of solving for the activity residing in a particular compartment was limited to the linear flow of activity through the body not allowing feedback (Skrable KW, 1974). Through the years, models have been developed to better represent the biological process and to include recirculation of material through the body before exiting. The advancement of biokinetic models has led to abandoning analytical representations and resorting exclusively to numerical computer calculations to solve the ever increasingly complex models (Polig E, 2001) (Pogliani L, 1996).

To evaluate the ICRP 78 hermaphrodite model, it is assumed that we will evaluate a single intake in which the compartments follow first order kinetics which can be described by a system of linear differential equations. The change in the amount of activity with respect to time shall be equal to the transfer rate matrix multiplied by the individual transfer rates between compartments.

$$\frac{dq}{dt} = \boldsymbol{Rq} \tag{4.1}$$

Where the constant matrix **R,** is the matrix of transfer rates with elements r_{ij} representing the fractional transfer rate from compartment *j* to compartment *i*. The elements $q_i(t)$ of the "state vector" **q**(t) of the n-compartment system represent the contents of compartment *i* at time *t*. In addition to biological transfer, a radionuclide with decay constant λ disappears with this rate from all compartments. Thus, physical decay and biological transfer combined yield:

$$\frac{dq}{dt} = \boldsymbol{Aq};\ \ \boldsymbol{A} = \boldsymbol{R} - \lambda \boldsymbol{I}; \mathbf{q}(0) = \boldsymbol{q}_0. \tag{4.2}$$

So that **q** is defined by a set of column vectors and **I** is the n*n identity or unit matrix. Without the loss of generality, it is assumed that at time t = 0 and time t_i the state of the system is known to be $\mathbf{q_0}$. This simply means that the calculation starts with known compartment contents. The solutions of equation (4.2) is completely analogous to the one-dimensional case

$$\boldsymbol{q}(t) = e^{At}\boldsymbol{q}_0 \tag{4.3}$$

where the matrix-exponential e^{At} is a matrix defined by its series expansion:

$$e^{At} = \sum_{i=0}^{\infty} \frac{(\mathbf{A}t)^i}{i!};\ \mathbf{A}^0 = \boldsymbol{I} \tag{4.4}$$

The definition in equation (4.4) is not always useful for a practical calculation because series may converge slowly. Birchall and James derived an algorithm for calculating the exponential based on the above series expansion and combined with a procedure of convergence acceleration (Birchall & James, 1989). The Birchall and James algorithm is what is used by Integrated Model for Bioassay Analysis IMBA and weighted likelihood Monte Carlo sampling WeLMoS to calculate the intake from bioassay data. However, the most common method of calculating the matrix exponential is by using eigenvalues and eigenvectors of $\mathbf{A}^{\mathbf{T}}$.

A theorem of linear algebra states that an n*n matrix **A** with linearly independent set of n eigenvectors can be decomposed by a similarity transformation into

$$\boldsymbol{A} = P\boldsymbol{\Lambda}\boldsymbol{P}^{-1} \tag{4.5}$$

Where **P** is the matrix who's n columns are formed by the n eigenvectors $\mathbf{p}_i$, $\mathbf{P}^{-1}$ is the inverse of **P**, and Λ is a diagonal matrix formed by the n eigenvalues λ_i, …, λ_n on the main diagonal and zero everywhere else:

$$\boldsymbol{A} = (\boldsymbol{p_1}, \ldots., \boldsymbol{p_n}) \begin{pmatrix} \boldsymbol{\lambda_1} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \boldsymbol{\lambda_n} \end{pmatrix} (\boldsymbol{p_1}, \ldots., \boldsymbol{p_n})^{-1} \tag{4.6}$$

With the eigenvalues and eigenvectors known, all functions of **A** can be calculated easily, because

$$\boldsymbol{A} = P\,F(\boldsymbol{\Lambda})\boldsymbol{P}^{-1} = \boldsymbol{P} \begin{pmatrix} \boldsymbol{F(\lambda_1)} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \boldsymbol{F(\lambda_n)} \end{pmatrix} \boldsymbol{P}^{-1} \tag{4.7}$$

If $F(A) = e^{At}$:

$$\boldsymbol{e^{At} = P\begin{pmatrix} e^{\lambda_1 t} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & e^{\lambda_n t} \end{pmatrix} P^{-1}} \quad \textbf{(4.8)}$$

And if $F(A) = A^{-1}$:

$$\boldsymbol{A^{-1} = P\begin{pmatrix} \frac{1}{\lambda_1} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & \frac{1}{\lambda_n} \end{pmatrix} P^{-1}} \quad \textbf{(4.9)}$$

The mathematical routines for calculating eigenvalues and eigenvectors are available in most mathematical software. The special situations of multiple eigenvalues or the case of not having a full set of n linearly independent eigenvectors exists is not discussed. With commonly used biokinetic models for radionuclides and the real numbers associated with the solutions these situations practically never occur.

Considering the solution given using equation 4.3 and 4.8, it is clear that $\lambda_i \leq 0$ for (t) approaching infinity the state vector **q** must remain finite. In cases of a stable element ($\lambda = 0$), one or more eigenvalues may be zero. If, after renumbering, we assume that the first m eigenvalues are zero, then the system settles on a non-zero state vector $\mathbf{q}_\infty$ for (t) going to infinity.

$$q_\infty = Bq_0; B = P\begin{pmatrix} I_m & 0 \\ 0 & 0 \end{pmatrix} P^{-1} \quad \textbf{(4.10)}$$

$\mathbf{I_m}$ is the m*n unit matrix. The eigenvectors in **P** have to be renumbered accordingly. Zero eigenvalues occur if the system has traps, i.e., it contains compartments that are irreversibly connected to their environment (Polig E, 2001).

So, in solving the complex biokinetic systems the intake and or activity in a specific compartment can be calculated using eigenvectors and eigenvalues as well as the series expansion method from Birchall and James (Birchall & James, 1989). This allows for the quick analysis of bioassay data to predict activity and ultimately calculate the dose.

4.2 Uncertainties in Bioassay Measurements

The propagated uncertainty in all measurements and analysis of bioassay data is needed to more accurately predict dose to the subject. Although there are large generalizations made in current biokinetic models, the collective uncertainty in bioassay data should be minimized to allow for a better fit of the data when using the maximum likelihood function. The improved fit of the multiple bioassay data sets will improve the predictive capability of the model. This enables an objective approach to determining whether or not the intake and calculated dose are consistent with the data (Marsh JW, 2008).

The uncertainty in bioassay measurements takes one of two forms (Type A or Type B) of counting errors. The Type A error represents the stochastic nature of radioactive decay measurement error that is associated with the detection of decay events. While Type B errors may be associated with: recovery rate in in-vitro and in-vivo samples, sample size variation, sample counting efficiencies, and variations of material biokinetics (Marsh, 1998). The uncertainty for the Durbin measurements performed was not documented in the literature afforded to us. A standard uncertainty of twice the square root was assigned as the standard uncertainty for all measurements.

4.3 Integrated Modules for Bioassay Analysis (IMBA)

IMBA, the Integrated Modules for Bioassay Analysis, is an internal dosimetry suite of software developed by the United Kingdom Health Protection Agency (UK-HPA). The IMBA software under license to Idaho State University by its developers is an extended research edition which allows more customizability. The IMBA software is capable of calculating activity in organs, and dose due to internally deposited organs due to their translocation kinetics. The biokinetic models of International Council on Radiation Protection (ICRP) and the National Council on Radiation Protection (NCRP) are capable of being incorporated into IMBA software to solve the activity and or dose in a specific organ given a known intake. Alternately, through the analysis of posterior biokinetic data following an intake, the bioassay data can be compared to the mode of uptake, and an estimated intake can be calculated. The advantage of IMBA over hand calculations or other programs is that it allows the analysis of multiple and different bioassay samples, either individually or simultaneously, to predict the intake. The calculation of predicted bioassay quantities, intake and doses can be calculated for up to 10 individual intake regimens, determined by the duration of the intake either acute or chronic, time of intake and route of entry (i.e. absorption, ingestion, inhalation or injection) (Birchall A, 2007).

The IMBA software under license to Idaho State University is an extended research edition, known as IMBA Professional Plus Academic Edition (IMBA-PPAE) (Version 4.1.49). This extended version of the software package allows a Bayesian fitting methodology that enables the calculation of intakes from bioassay analysis. Furthermore, IMBA-PPAE allows the user to operate in future model mode. Future mode allows the

creation of custom biokinetic models and the ability to add, subtract, and change model parameters of current ICRP, NCRP, or custom models.

The ICRP-78 strontium model for hermaphrodites was used due to its applicability to either sex in the case of the two cohorts of monkeys studied. Subsequently the ICRP model was designed and input into the IMBA-PPAE biokinetic model builder. To calculate the retention functions of the male test group, a composite of the model monkey was generated. The composite retention functions were made by combining all data for the male cohort. When building the composite dataset, individual monkey data that overlapped on the same day was averaged. Once the data was composited, and after being organized into an appropriate IMBA input file the retention for the selected compartments was analyzed by inputting the known intake, and calculating the activity based on the ICRP model. The difference was then calculated and compared to the actual measured data to make a judgment as to the accuracy of the prediction.

The IMBA-PPAE software utilized the maximum likelihood fitting method to determine the best fit of the retention curve, resulting in the calculation of the best estimate of the intake given a set of bioassay data as previously discussed. Using the maximum likelihood method, IMBA-PPAE calculates the best intake (I) from the bioassay data ($m_i t_i$) such that the product of (I) and f(t) that best fits the data. In this case, were f(t) represents the fitted retention function of the bioassay data (James 2005). The difference between the predicted intake and the known intake was minimized. The relative goodness of fit using the maximum likelihood curve compared to the predicted

data and systemic model was determined by calculating the chi-squared (χ^2) as outlined in the following section.

4.4 IMBA Statistics

IMBA-PPAE utilizes the chi-squared statistic to evaluate the "goodness of fit" of biokinetic models to bioassay data. The chi-square statistic (χ^2) is a measure of the difference between the values in the measured time dependent series data and that of the model predicted curve. If each measurement is assumed to have a normal distribution, the value of χ^2 is calculated as follows (Doerfel H A. B., 2006).

$$\chi^2 = \sum\left(\frac{(Im(t)-M(t))^2}{M(t)}\right) \quad \textbf{(4.14)}$$

Where the product $I_m(t)$ is the predicted value. In IMBA, when the predicted values are sent to multiple types of bioassay data simultaneously, the overall χ^2 is equal to the sum of the calculated χ^2 for each data set. When evaluating Equation 4.14 for the chi-squared statistic, it becomes evident that a value of zero would indicate a perfect fit. In this data set, it is highly improbable that such a fit will be achieved due to the compositing of the data set and because of the uncertainties related with the data. However, a decrease in the χ^2 statistic when comparing the modified model parameter and the default model, may indicate an improved model fit. Inversely, if the model predictions inadequately describe the measured data, the calculated value of the chi-square statistic will increase from the default model as well as the theoretical value of chi-square distribution.

4.5 IMBA Uncertainty Analyzer

The use of the integrated model for bioassay analysis uncertainty analyzer (IMBA-UA) standalone module provides a method of analyzing bioassay data and calculating the intake and ultimately the dose when the varied parameters are modeled in IMBA. The IMBA-UA module uses Bayesian statistics to analyze and fit the bioassay data and is a widely used and accepted method in internal dosimetry calculations (Miller G M. H., 2002) (Miller G I. W., 2000). Bayes theory is used to combine *a priori* knowledge about the value of the intake with the observed bioassay data to produce an *a priori* posterior probability distribution of the intake (Birchall A, 2007). Where an *a priori* piece of information is known relative to the intake, a Bayesian probability distribution function of the intake can be ascertained and subsequently can be used in conjunction with bioassay measurements to generate an improved posterior probability distribution of the intake (Birchall A, 2007).

Building upon the Bayesian analysis method, IMBA uses its companion module, the uncertainty analyzer (UA) to perform more complex Bayesian analysis needed for predicting posterior probability distribution for biokinetic model parameters. The UA uses a Monte Carlo sampling method termed the Weighted Likelihood Monte Carlo Sampling Method (WeLMoS) which relies on a weighted Latin Hypercube method to calculate the Bayesian posterior distributions of parameters and dose. The WeLMoS method works by first generating random samples from the prior distribution of biokinetic parameters using Monte Carlo sampling protocols. Subsequently, each vector is weighted according to its likelihood (i.e. the probability of the data given the vector of parameters and the intake) and orders them in an increasing order of χ^2 (Puncher &

Birchall, A Monte carlo method for calculating Bayesian uncertainties in internal dosimetry, 2008). In essence, the parameters are weighted according to how well the sampled intake and parameters fit the data (Puncher & Birchall, The autocorrelation coefficient as a tool for assessing goodness of fit between bioassay predicitons and measurment data, 2008). The weighted values are then used to calculate posterior distributions of intake and model parameters.

The uncertainty analyzer, as used in this project, is used in conjunction with IMBA-PPAE in order to implement the WeLMoS method. As a first step in the process, a sample matrix is constructed by the UA from an *a priori* probability distribution defined by the user. The uncertainty analyzer then uses IMBA-PPAE to solve the pertinent biokinetic models in order to calculate intake and bioassay predictions over the required measurement times. This is accomplished by the uncertainty analyzer communicating directly with the critical subroutines contained in IMBA-PPAE, thus allowing for intake and dose calculations to be derived by Monte Carlo simulations. In the next stage of the process, the user specifies a range of discrete intakes or parameters that is assumed to contain the range of intake in the posterior distribution. Finally, intakes and bioassay predictions from the previous steps are used to calculate the weighted likelihood and posterior distributions for intake and model parameters (Puncher and Birchall 2008).

4.6 IMBA Future Mode

The main objective of this study is to derive a simplified ^{90}Sr biokinetic model which is based on other bone seeking radionuclides. To determine if the model was improved over the default ICRP 78 ^{90}Sr systemic model, analysis was performed to

determine which model obtained an improved fit to the bioassay data, and improved the predictive capabilities of the calculated intake and long term skeletal retention. To accomplish this task, IMBA-PPAE provides a programming environment called future mode, in which customized models can be designed and saved as source files to be investigated using the uncertainty analyzer an add on program. Some radionuclides have pre-loaded future mode systemic biokinetic models based on the ICRP 60 series that allows the user to adjust inter-compartmental transfer rates with the uncertainty analyzer program. However, IMBA-PPAE future mode did not contain a pre-exiting model in the case of ICRP 78 ^{90}Sr hermaphrodite model. In response one was built and implemented into the IMBA-PPAE software.

A custom model was created in IMBA-PPAE future mode to incorporate the transfer rates and kinetics of strontium in the body. The model shown in Figure 14 was implemented into IMBA the future mode biokinetics tab Figure 15 with transfer rates as shown in Table 3. The developed systemic ICRP 78 model allows for other models to be attached such as the HRTM and HATM models.

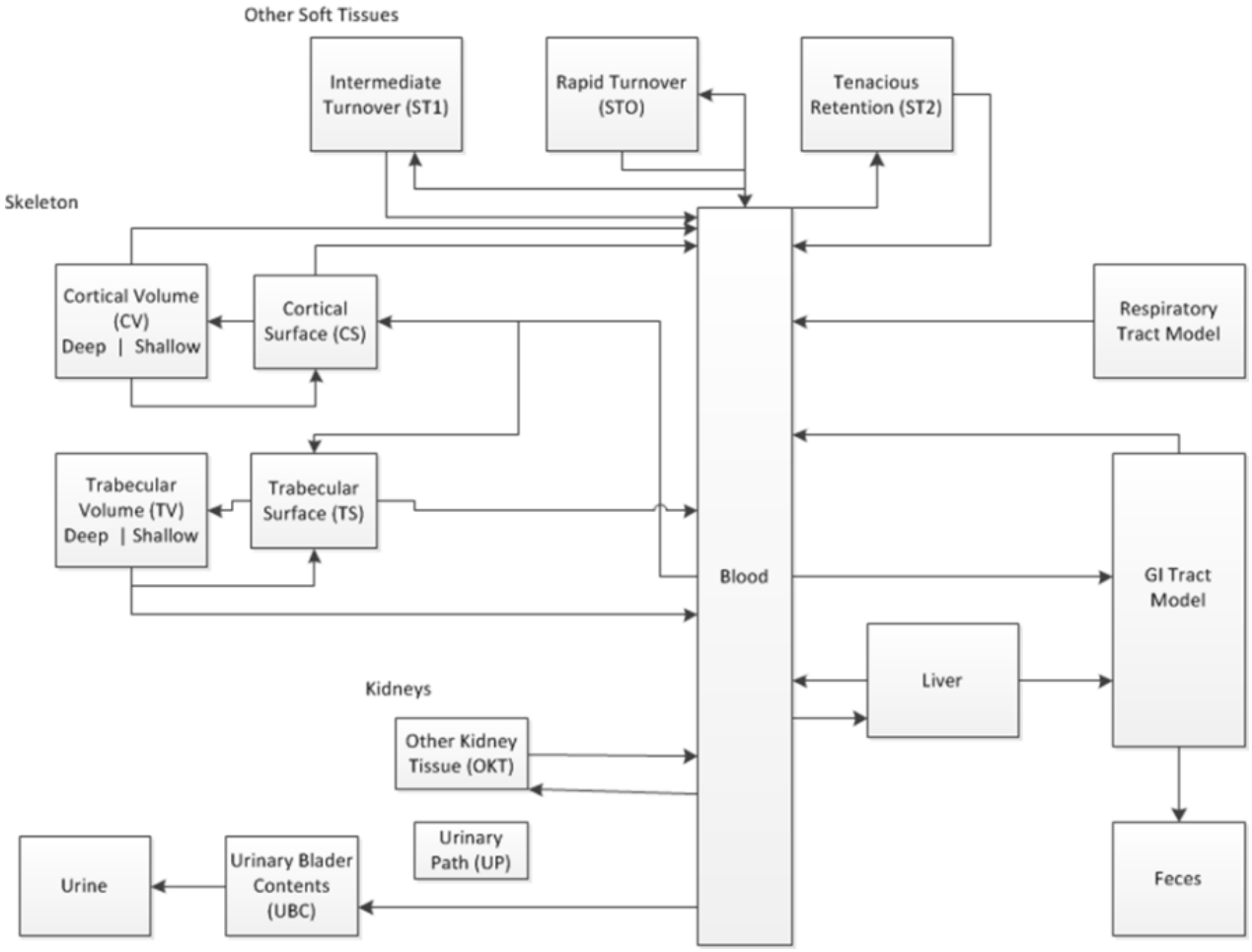

Figure 14 ICRP Publication 78 Default Model

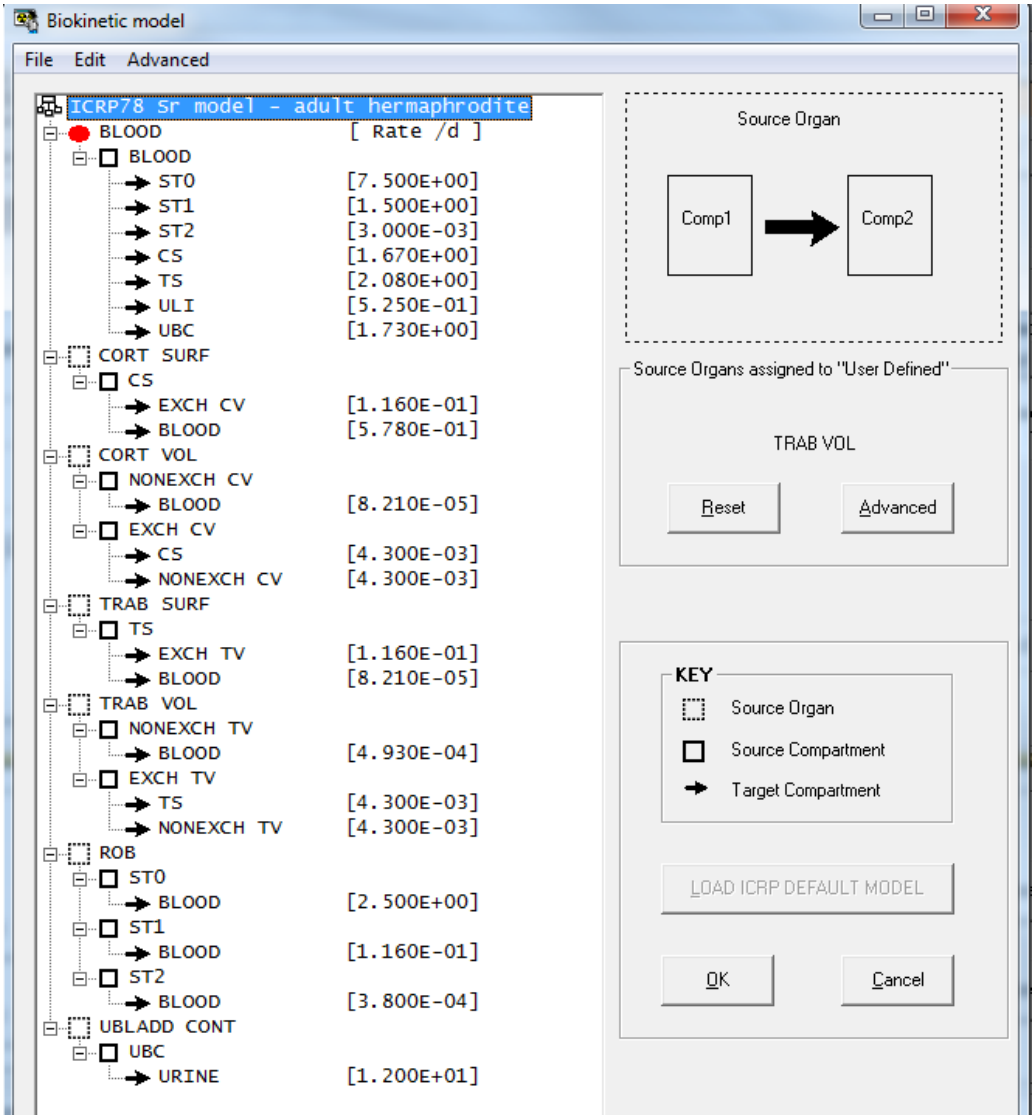

Figure 15. IMBA Future Mode Screen Shot

Table 3. ICRP 78 Sr-90 Default Transfer Parameters

Starting Compartment	Ending Compartment	Default Transfer Rate (d^{-1})
BLOOD	ST0	7.50
BLOOD	ST1	1.50
BLOOD	ST2	$3.00\ 10^{-3}$
BLOOD	CORTICAL SURFACE	1.67
BLOOD	TRABECULAR SURFACE	2.08
BLOOD	RC CONTENTS	$1.16\ 10^{-1}$
BLOOD	URIN BLADDER CONT	$5.78\ 10^{-1}$
CORTICAL SURFACE	EXCH CORT VOL	$1.16\ 10^{-1}$
CORTICAL SURFACE	BLOOD	$5.78\ 10^{-1}$
NONEX CORT VOL	BLOOD	$8.21\ 10^{-5}$
EXCH CORT VOL	CORTICAL SURFACE	$4.30\ 10^{-3}$
EXCH CORT VOL	NONEX CORT VOL	$4.30\ 10^{-3}$
TRABECULAR SURF	EXCH TRAB VOL	$1.16\ 10^{-1}$
TRABECULAR SURF	BLOOD	$8.21\ 10^{-4}$
NONEX TRAB VOL	BLOOD	$4.93\ 10^{-4}$
EXCH TRAB VOL	TRABECULAR SURFACE	$4.30\ 10^{-3}$
EXCH TRAB VOL	NONEXCH TRAB VOL	$4.30\ 10^{-3}$
ST0	BLOOD	2.50
ST1	BLOOD	$1.16\ 10^{-1}$
ST2	BLOOD	$3.80\ 10^{-4}$
URIN BLADDER CONT	URINE	12.0

When the gastrointestinal tract model is incorporated as the intake pathway, material must travel through the stomach (ST) region to the small intestine (SI) where it can then move into the transfer compartment as shown in Figure 16 or pass into the upper large intestine (ULI). The gastrointestinal tract model is added into the systemic model

shown by Krage et al. to best represent the biokinetics of nonhuman primates (Krage). The model structure developed model allows interfacing with other models such as the GI-Tract Model (as shown in Figure 14). It assumes that all of the internalized radionuclide enters directly into the transfer compartment. Once the radionuclide is in the transfer compartment, it follows the biokinetic model through the body.

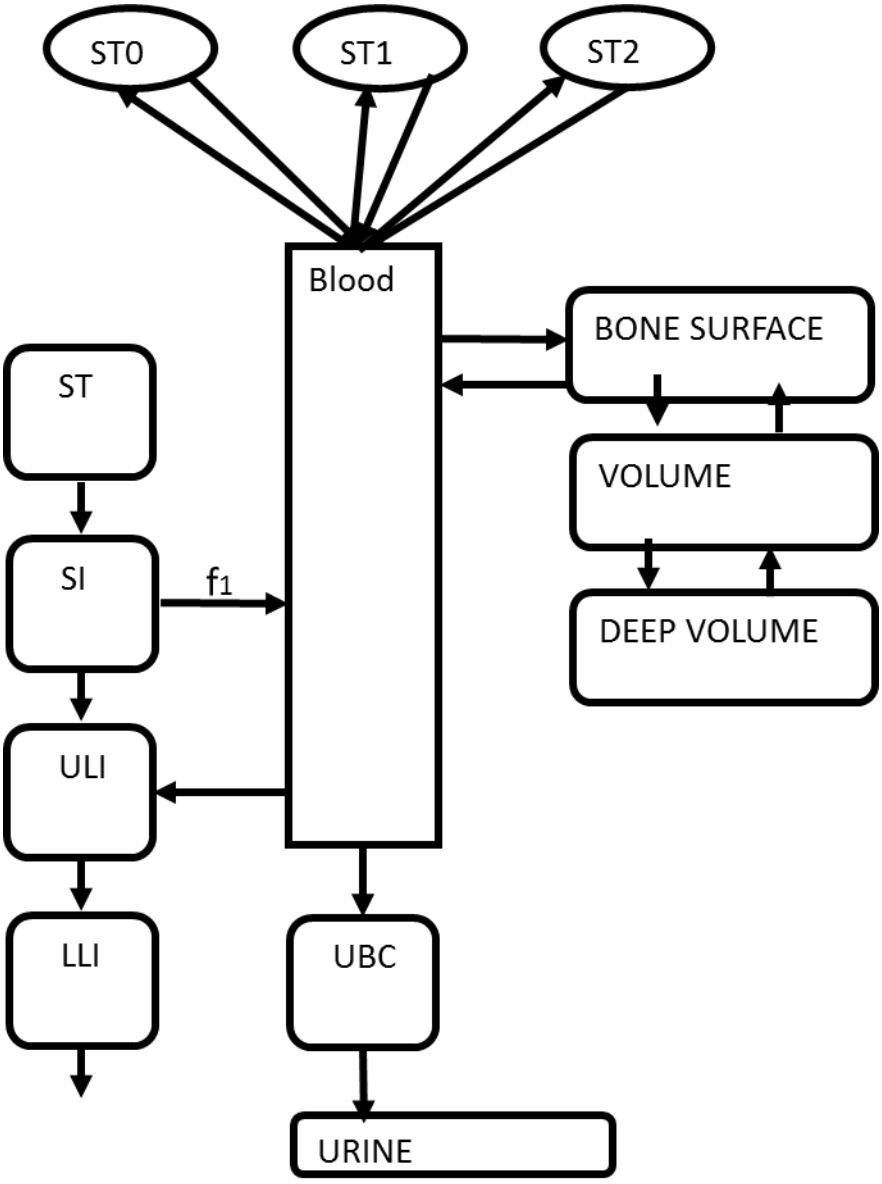

Figure 16 Krage Model C with ICRP 30 Gastrointestinal Tract Model

4.7 ICRP 30 Gastrointestinal Tract Model and Krage Model C Systemic Model

When evaluating the ^{90}Sr hermaphrodite model created in IMBA-PPAE future mode, as well as the models proposed by Krage using the uncertainty analyzer, an issue arises because the UA restricts the user to vary only nine model parameters at any one time. While it is likely that the alteration of some model parameters is unnecessary due to their negligible effect on the transfer kinetics, selecting the model parameters that have the largest effect on the predicted bioassay data as well as the ones that have the most physiological significance is appropriate for finding rapid solutions in these types of analyses. A sensitivity analysis also aids in identifying the physiological processes and pathways that are associated with the transfer rates that heavily influence the bioassay predictions (Luciani A, 2001). In the case of the three models tested all, parameters involving the bone compartment were able to be modified simultaneously. However, it was still pertinent to perform a sensitivity analysis of the system.

A sensitivity analysis of the model was conducted to establish which of the available parameters most influenced the modes predictive capability. Many methods have been proposed for evaluating sensitivity of model parameters in general applications (Hamby 1995). A differential sensitivity analysis was chosen for this project, in part because of prior success shown in other biokinetic models (Luciani et. al. 2001).

In the differential method, the partial derivative of the mathematical expression is what describes the transfer kinetics between compartments in the model. The partial derivative of the dependent variable (excretion or retention rate) is calculated with respect

to the independent variable, which is then used to calculate a sensitivity coefficient for the independent variable (Luciani A, 2001). The sensitivity coefficient (S_i) is defined as the ration of the relative exchange of the intake or retention rate (u) to the relative change of the respective model parameter (λ_i).

$$S_i = \frac{du}{d\lambda_i} * \frac{\lambda_i}{u} = \frac{\Delta u}{\Delta \lambda_i} * \frac{\lambda_i}{u} \quad \textbf{(4.15)}$$

Equation 4.15 was modified to determine S_i using the default systemic model predicted values for activity retained in the whole blood, whole-body, and skeleton to determine intake as follows:

$$S_i = \frac{\Delta I}{\Delta \lambda_i} * \frac{\lambda_i}{I} \quad \textbf{(4.16)}$$

Where (I) is the intake predicted using the default parameter values for activity in whole blood, whole-body, and skeleton at various times post-injection and (ΔI) is the change in the intake due to the change in the altered parameter ($\Delta\lambda_i$). Therefore, if a model's transfer rate is increased by 10% (i.e. $\Delta\lambda_i = 0.1*\lambda_i$), ($S_i$) can be expressed as follows:

$$S_i = 10 * \frac{\Delta I}{\mathrm{I}} \quad \textbf{(4.17)}$$

A change of 10% was chosen as a convenient value to use in the sensitivity analysis since the effect of intake due to the change in the transfer rate was not affected by small rounding errors (Luciani et al. 2001).

4.8 Biokinetic Hyper-modeling

To implement the WeLMoS Monte Carlo method, the IMBA-PPAE future mode and the three proposed models were constructed and loaded. Subsequently, all the bone

parameters and the most sensitive parameters as determined from the sensitivity analysis were selected to be varied in the uncertainty analyzer. A log-uniform distribution was specified for each parameter modeled. The range of the sampling regime was 0.01 to 100 times the value of the default parameters as suggested in the IMBA software manual. The Latin hyper-cube method was selected as a random sampling method and was used to from an [n*N] sample matrix, where (N) is the desired number of iterations and (n) is the number of biokinetic parameters to be varied (Puncher Birchall 2008). The number of simulations (N) in this study was selected to be $1*10^6$ for each set of iterations for each of the three systemic models tested.

4.9 Optimization of Intake and Skeletal Retention Prediction

After completion of WeLMoS sampling, (N) sets of varied parameters and their associated intake were calculated and ordered from smallest to largest value of the chi-square statistic. The percent relative difference between the predicted and known intake was calculated using Equation 4.18.

$$Percent\ Relative\ Difference = \left|\frac{(Measured - Predicted)}{\left(\frac{Measured + Predicted}{2}\right)}\right| * 100\% \qquad \textbf{(4.18)}$$

A data reduction method was put into place to evaluate only model parameters that predicted the intake within 5% and resulted in a chi-squared value in the lowest 1%. However, a practical decision rule was established that the best model parameters were not only those that predicted the intake within 5% but also reduced the difference between predicted and measured activity in the skeleton and whole-body count data in

order to provide the least overall relative difference between predicted and measured values. In the event the model was not able to meet the selection criteria of a chi-squared value in the lowest 1%, the model with the best predicted intake was selected.

Chapter 5 RESULTS AND DISCUSSION

5.1 Comparison of Default Model Predictions for the Male Composite Cohort and models A, B, & C.

The intent of this study was to obtain a simplified model for the biokinetics of i.v. injected strontium that would perhaps improve modeling endeavors. A further rationale for this simplification was based on the level of detail in the available NHP data set. A composite set of data derived for modeling purposes was used in this study because of similar injected activities in the subjects as shown in Table 4.

Table 4 Activity in the skeleton at sacrifice and whole-body of the composite male cohort.

Skeleton		Whole-body Counts	
Time (Days)	Activity(MBq)	Time (Days)	Activity(MBq)
728	0.81	37.00	2.20
740	0.74	85.00	1.89
1742	0.61	359.00	1.41
2313	0.27	407.00	1.23
2835	0.17	522.00	1.03
4599	0.44	727.00	0.93
5232	0.25	797.00	0.87
5860	0.19	825.00	0.89
		1018.00	0.74
		1204.00	0.62
		1456.00	0.56
		1661.00	0.49
		1814.00	0.46
		1920.00	0.43
		2241.00	0.38
		2458.00	0.34
		2664.00	0.34
		2900.00	0.32
		3090.00	0.31
		3257.00	0.29
		3579.00	0.28
		4098.00	0.26
		4525.00	0.23
		4889.00	0.20
		5272.00	0.21
		5860.00	0.20

The development of three models (A, B, & C), and default model parameters were modified through the use of Markov Chain Monte Carlo and IMBA-PPAE. The parameters selected for modification were all those associated with transfer to the bone

from the blood, bone to bone, and excretion pathways. The other compartments, which were based on other organs, remained the same because of lack of data to justify their modification. The result of the Monte Carlo calculation resulted in the transfer rates shown in Table 5.

Table 5 Derived Transfer rates of systemic models A, B, and C

Model A			Model B			Model C		
Source	Target	Rate	Source	Target	Rate	Source	Target	Rate
Blood	ST0	7.5	Blood	ST0	7.5	Blood	ST0	7.5
Blood	ST1	1.5	Blood	ST1	1.5	Blood	ST1	1.5
Blood	ST2	0.003	Blood	ST2	0.003	Blood	ST2	0.003
Blood	BONE SURFACE	33.8	Blood	BONE SURFACE	1.672	Blood	BONE SURFACE	3.788
Blood	ULI	0.29	Blood	ULI	0.1993	Blood	ULI	0.1586
Blood	UBC	3.184	Blood	UBC	5.821	Blood	UBC	10.79
BONE SURFACE	BLOOD	0.04741	BONE SURFACE	BLOOD	0.001209	BONE SURFACE	BLOOD	0.001756
BONE SURFACE	VOLUME	0.005799	BONE SURFACE	VOLUME	0.000155	BONE SURFACE	VOLUME	0.000242
VOLUME	BLOOD	0.000124	VOLUME	SURFACE	4.18E-05	VOLUME	SURFACE	2.27E-05
VOLUME	SURFACE	0.00299				VOLUME	DEEP VOLUME	2.17E-07
			ST0	BLOOD	2.5			
ST0	BLOOD	2.5				ST0	BLOOD	2.5
			ST1	BLOOD	0.116			
ST1	BLOOD	0.116				ST1	BLOOD	0.116
			ST2	BLOOD	0.00038			
ST2	BLOOD	0.00038				ST2	BLOOD	0.00038
			UBC	URINE	12			
UBC	URINE	12				UBC	URINE	12
						DEEP-VOLUME	VOLUME	2.99E-05

Mote Carlo simulations for all three models were tested against the parameter selection criteria. It was determined in the model evaluation process that, model A, was unable to achieve a prediction within 5% of the known intake and with a χ^2 in the lowest 1% in the allotted number of iterations, as seen in Table 6. In response to this outcome, the model parameters selected were those that most accurately predicted the intake with a χ^2 in the lowest 1%. As a result, it was concluded that model A, failed to meet the criteria and accurately predict the data.

Table 6 Evaluation of ICRP-78 model and model A, B, & C using the composite male cohort data.

	Known Intake (MBq)	Calculated Intake (MBq)	Absolute Difference Intake	Absolute Difference Skeleton (Sum)	Absolute Difference Whole-body (Sum)	Total
ICRP-78	7.6	1.38	1.39	10.16	35.38	46.92
Model A	7.60	2.77	9.31×10^{-1}	8.31	24.4	33.6
Model B	7.60	7.25	4.74×10^{-2}	8.31	6.59	14.5
Model C	7.60	7.65	6.69×10^{-3}	1.98	2.38	4.62

Model B, was a simple two-compartment bone model. Our evaluation produced the transfer rates shown previously. Evaluating the transfer rates, it can be seen that the bone volume acts as a long-term reservoir for strontium in this model. The rates are consistent in magnitude with those suggested by the ICRP alkaline earth element model (ICRP, 1997). Looking at the overview of the three models tested, we can see that model B predicts the intake of known activity in the composite cohort within 5%, but grossly under predicts the activity in the skeleton in the long term.

Model C is a three-compartment bone model in which only one compartment transfers material between bone compartments and the transfer compartment. Model C parameters predicted the intake to within a fraction of a percent and enhanced the prediction of ^{90}Sr activity in bone long term over model B by a factor of 4 when comparing the absolute differences. The main difference between the two models is the inclusion of a deep bone volume in model C. Physiologically, deep bone volume represents strontium incorporation into bone accretion. Since generating new bone is a slow process after the developmental stages of the skeleton, the transfer rate into the deep volume compartment appears to be necessarily slow. Once cancellous bone is formed, it may not undergo remodeling throughout the life of the subject, this results in a slow feedback mechanism into the volume compartment (ICRP, 1997). Given these observations, it appears that quantitatively, model C best describes the intake and long term skeletal retention in the composite cohort. When comparing model C with the default 78 model, the sum of the absolute difference between predicted and measured values for each data point of activity in the skeleton and whole-body count data was 5 and 47 respectively, resulting in a better prediction for model C. Mechanistically, the

ICRP 78 model and model C are similar, in that the exchangeable and nonexchangeable model structure work similarly to that of this paper's model of volume and deep volume compartments. However, the limitations of the NHP data did not justify breaking down the compartment model any further.

It appears that model C does in fact predict bone activity as a function of time better than the ICRP 78 default model by a factor of 5 when comparing the absolute differences. However, this is expected and circular because model C parameters were derived using the composite data set. To independently test whether model C better predicts the retention of strontium in the body, 4 cases were set aside as a validation cohort. The subjects in the validation cohort consisted of four male monkeys that were injected with different activities and sacrificed at different times post injection.

Using the set-aside case data and considering the prediction overall of strontium intake for model C and the default ICRP 78 model as provided in Table 7, we can see that the overall relative difference is lower for model C, implying that model C is a better indicator of intake. Evaluating the cases independently, we see that the ICRP default model predicted the activity better in cases R310M and R313M, which both had very short time between injection and sacrifice. The author reminds the reader that model C was developed using the composite data set, which included cases with analysis from 728 days to 5,800. So it is no surprise that short-term predictions are weak. Another issue that could lead to the poor early prediction is the number of data points used to make the prediction. When considering the simpler model, model C better predicts the intake over the ICRP 78 model by a factor of two.

Table 7 Predicted intake of validation cohort using model C and ICRP-78 systemic models.

			Predicted Intake			
Case #	Time Post Injection (days)	Injected Activity (Bq)	ICRP-78 Predicted Injected Activity (Bq)	Model C Predicted Injected Activity (Bq)	Relative difference (ICRP-78 predicted to measured)	Relative difference (Model C to measured)
R61M	5373	4.35×10^6	5.40×10^5	4.13×10^6	1.56	0.05
R62M	5853	6.23×10^6	3.10×10^5	2.62×10^6	1.81	0.82
R310M	67	3.31×10^6	3.51×10^6	5.61×10^6	0.06	0.52
R313M	150	1.65×10^6	1.24×10^6	2.55×10^6	0.29	0.43
				Sum	3.71	1.81

It is of interest to calculate the amount of activity residing in the skeleton, as it is the organ of concern. To do so, the subjects were analyzed at sacrifice to determine the activity residing in the skeleton. Testing the models, the predicted activity in skeleton was calculated at the times of sacrifice. The results of Model C and the ICRP 78 systemic model are provided in Table 8. It is observed in Table 8, that Model C predicted the activity in skeleton better than the ICRP systemic model overall by a factor of two. The individual cases show a similar trend to the intake predictions in that the short term were not both improved. Case R313M was not improved, however, case R310M was improved in skeletal prediction although it did not improve in the ability to predict intake. However, since the ICRP model was developed for humans, it is reasonable to assume that it may not accurately describe what the biokinetics of nonhuman primates.

Table 8 Predicted activity in the skeleton from a known intake of ^{90}Sr at sacrifice of the test cohort using systemic model C and ICRP-78.

		Predicted Activity In Skeleton				
Case #	Time Post Injection (days)	Skeletal Activity (Bq)	ICRP-78 Predicted Skeletal Activity (Bq)	Model C Predicted Skeletal Activity (Bq)	Relative difference (ICRP-78 predicted to measured)	Relative difference (Model C to measured)
R61M	5373	$1.08x10^5$	$8.15x10^5$	$1.14x10^5$	1.53	0.06
R62M	5853	$6.85x10^4$	$8.30x10^5$	$1.57x10^5$	1.70	0.78
R310M	67	$2.11x10^6$	$6.30x10^5$	$7.77x10^5$	1.08	0.92
R313M	150	$4.60x10^5$	$5.31x10^5$	$3.48x10^5$	0.14	0.28
				Sum	4.45	2.04

5.2 ICRP 78 ^{90}Sr Systemic Model and Krage Model C Evaluation and Optimization

The proposed model transfer rates in Table 9 were optimized by fitting the whole-body counts and skeletal data from the nonhuman primate injection studies. The intake calculations from the fit were 0.770, 4.492, and 3.033 MBq as calculated by IMBA for the different modeling approaches: ICRP, Krage male model, and the modified Krage model respectively. Inputting the known injection activity into IMBA, the retention was predicted in the whole-body for each of the models represented in Figure 17. It is clear from Figure 17 that the ICRP-78 model largely over predicted the activity residing in the body at all points in time. When evaluating the Krage model, which was developed for male NHP, it is seen that the model has a small negative bias in the prediction of the amount of activity residing in the body. The reason for this difference most likely is the physiological difference between male and female development. We believe that this difference could be associated with the observation that females take longer to reach peak

bone mass density and thus over time are able to accumulate more strontium in the body. The evaluation of the modified Krage model predicted the activity residing in the body accurately at all points because it was the data set for which the model was optimized. The major change in the modified Krage model is the transfer rate from the deep volume to the volume compartment. This parameter difference is directly related to the slowed bone remodeling rate of the female skeleton and bone loss at the onset of osteoporosis.

Table 9 Krage Model C Biokinetic Parameters and Krage Modified Parameters for Female Nonhuman Primates

Krage Model			Modified Krage Model		
Source	Target	Rate (d^{-1})	Source	Target	Rate (d^{-1})
Blood	ST0	7.5	Blood	ST0	7.5
Blood	ST1	1.5	Blood	ST1	1.5
Blood	ST2	3.00×10^{-3}	Blood	ST2	3.00×10^{-3}
Blood	BONE SURFACE	3.788	Blood	BONE SURFACE	1.108
Blood	ULI	1.59×10^{-1}	Blood	ULI	1.86×10^{-2}
Blood	UBC	10.79	Blood	UBC	1.824
BONE SURFACE	BLOOD	1.76×10^{-3}	BONE SURFACE	BLOOD	1.80×10^{-3}
BONE SURFACE	VOLUME	2.42×10^{-4}	BONE SURFACE	VOLUME	2.03×10^{-4}
VOLUME	SURFACE	2.27×10^{-5}	VOLUME	SURFACE	2.47×10^{-6}
VOLUME	DEEP VOLUME	2.17×10^{-7}	VOLUME	DEEP VOLUME	2.95×10^{-8}
ST0	BLOOD	2.5	ST0	BLOOD	2.5
ST1	BLOOD	0.116	ST1	BLOOD	0.116
ST2	BLOOD	3.80×10^{-4}	ST2	BLOOD	3.80×10^{-4}
UBC	URINE	12	UBC	URINE	12
DEEP VOLUME	VOLUME	2.99×10^{-5}	DEEP VOLUME	VOLUME	7.98×10^{-6}

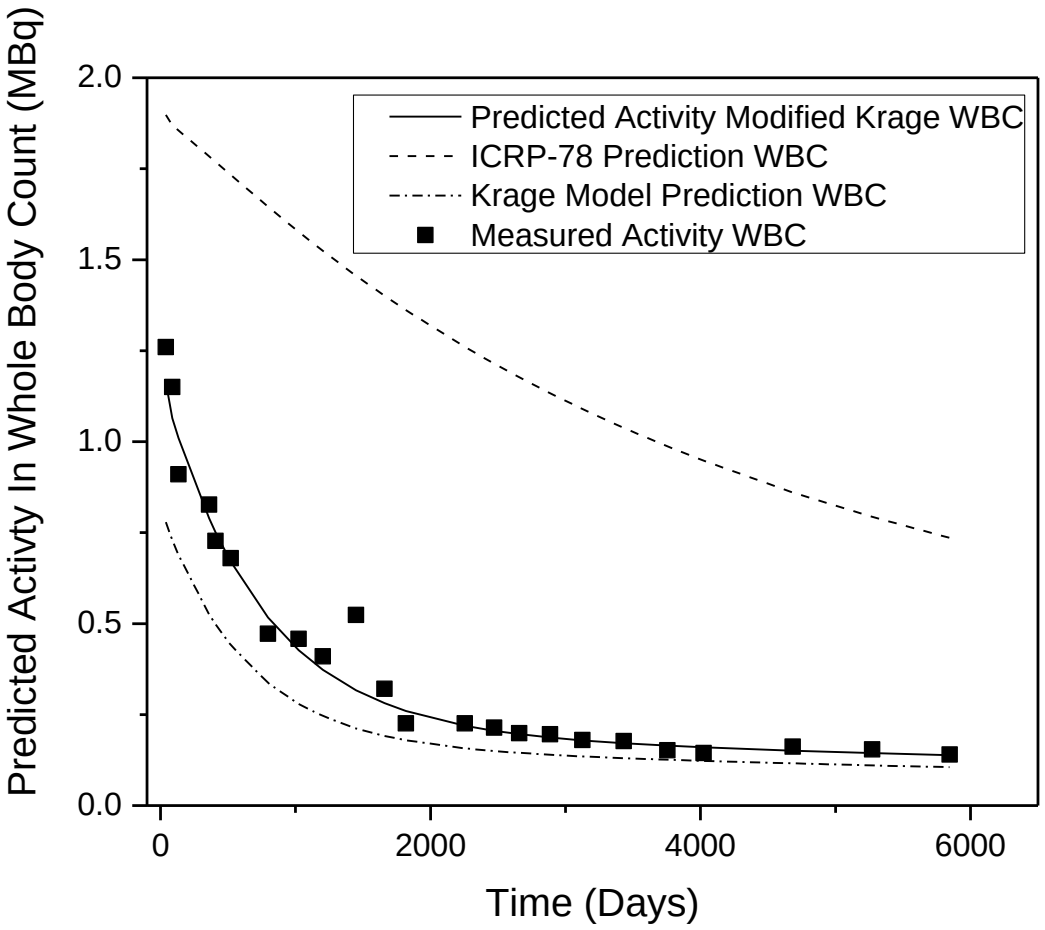

Figure 17 Whole-body Count Predictions for Female NHP Cohort

Skeletal concentrations from the three models were predicted using IMBA for the amount of strontium residing in the skeleton at time of sacrifice. The ICRP-78 model, at time of sacrifice, predicted higher than the measured value shown in Figure 3. The high prediction would be expected based on the high magnitude of whole-body counting data, since the majority of strontium is found in the skeleton. The Krage male NHP model slightly under predicts the activity in skeleton at sacrifice similar to that of the whole-body count data. The result of the Krage model was expected not to predict biokinetics

accurately as it was developed for use with male NHP; not females. The Krage model modified for female NHP, accurately predicted the intake to within 1% as by design.

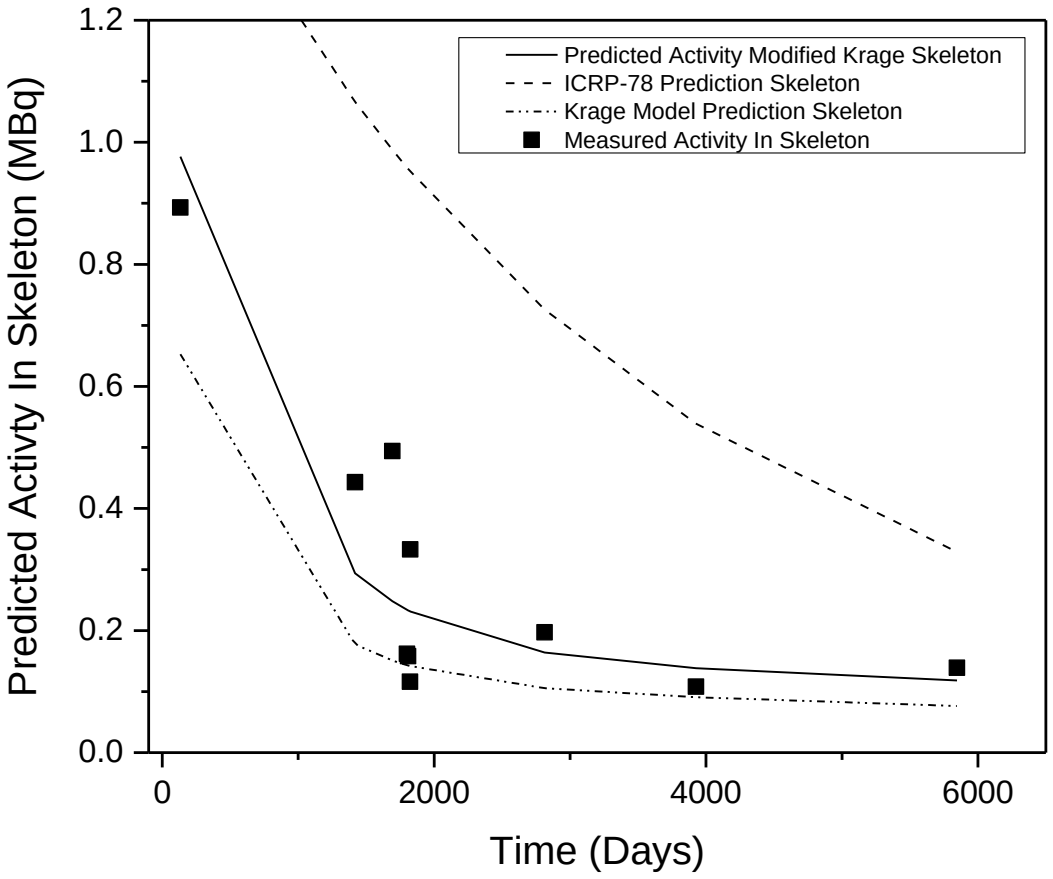

Figure 18 Skeletal Predictions of Krage Male NHP Model, ICRP 78, and Modified Krage for Female NHP's

5.3 Test Case Evaluation

After analyzing the intake predictions of the six female cases tested as seen in Table 10, it was evident that all but one case was improved when comparing the modified Krage model to the ICRP-78 model. Further analyzing case R306F, it is evident that the skeletal ^{90}Sr concentration prediction in Table 11 was also better predicted by ICRP 78. The main feature standing out in this case is that there was a very short-term to sacrifice in this case. The female NHP data range did not encompass this period of time. The Krage model, which was optimized for male NHP, also predicted intake better in all but case R306F. Again, looking at the range at which the Krage male NHP model encompassed, it did not contain short times to sacrifice cases.

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Table 10 Test Case Analysis of Intake for Proposed Sr-90 Systemic Models in Female NHP's

	Predicted Intake of Test Cases				Absolute Relative Difference		
Case #	Measured (Bq)	ICRP-78 (Bq)	From Krage (Bq)	Modified Krage (Bq)	ICRP-78	From Krage	Modified Krage
R21F	$1.83\ 10^{6}$	$4.09\ 10^{5}$	$2.89\ 10^{6}$	$2.18\ 10^{6}$	1.27	0.45	0.17
R32F	$2.26\ 10^{6}$	$6.92\ 10^{5}$	$5.19\ 10^{6}$	$3.96\ 10^{6}$	1.06	0.79	0.55
R306F	$2.48\ 10^{6}$	$2.36\ 10^{6}$	$4.84\ 10^{6}$	$2.82\ 10^{6}$	0.05	0.65	0.13
R38F	$1.85\ 10^{6}$	$1.27\ 10^{5}$	$1.01\ 10^{6}$	$7.40\ 10^{5}$	1.74	0.59	0.86
R39F	$1.85\ 10^{6}$	$8.45\ 10^{4}$	$6.44\ 10^{5}$	$4.81\ 10^{5}$	1.83	0.97	1.18
R40F	$2.60\ 10^{6}$	$3.67\ 10^{5}$	$8.95\ 10^{5}$	$5.85\ 10^{5}$	1.51	0.98	1.27

Table 11 Case Analysis of Skeletal Retention in Female NHP's

		Predicted Skeletal Activity				Absolute Relative Difference		
Case #	Time Post Injection (Days)	Measured (Bq)	ICRP-78 (Bq)	From Krage (Bq)	Modified Krage (Bq)	ICRP-78	From Krage	Modified Krage
R21F	6449	$7.82\ 10^{4}$	$1.71\ 10^{5}$	$4.38\ 10^{4}$	$6.84\ 10^{4}$	0.74	0.56	0.13
R32F	7168	$1.25\ 10^{5}$	$1.77\ 10^{5}$	$5.09\ 10^{4}$	$8.04\ 10^{4}$	0.35	0.84	0.43
R306F	14	$1.41\ 10^{6}$	$1.16\ 10^{6}$	$6.12\ 10^{5}$	$7.90\ 10^{5}$	0.19	0.79	0.56
R38F	3411	$4.00\ 10^{4}$	$3.78\ 10^{5}$	$5.89\ 10^{4}$	$9.01\ 10^{4}$	1.62	0.38	0.77
R39F	5650	$1.43\ 10^{4}$	$2.11\ 10^{5}$	$4.75\ 10^{4}$	$7.32\ 10^{4}$	1.75	1.07	1.35
R40F	99	$1.61\ 10^{5}$	$1.30\ 10^{6}$	$5.86\ 10^{5}$	$8.72\ 10^{5}$	1.56	1.14	1.38

Skeletal predictions for ICRP-78 and the male and female optimized Krage model are mixed. There are two cases in which the ICRP-78 predicts better than that of the male or female models optimized for NHP. However, the majority of the modified Krage model cases predicted the final activity residing in the skeleton better than that of the ICRP-78 systemic model. Again, case R306F was better predicted by ICRP-78 as well as case R32F. The explanation of this is that neither of these cases were encompassed by the data range upon which the male or female NHP Krage models were developed.

Evaluating the whole-body count data in Table 12, it can be seen that the data mimics the trend seen for the intake predictions. In all but case R306F, the modified Krage model better depicts the activity residing in the body at time of measurement. Comparing the Krage and modified Krage model, it can be seen in Table 13 that the overall whole-body count prediction is better by 0.24 for the modified Krage model.

Table 12 Whole-body Count Comparison

	Whole-body Count Absolute Difference		
	ICRP-78	From Krage	Modified Krage
R21F	1.28	0.44	0.18
R32F	1.07	0.76	0.51
R306F	0.07	0.67	0.14
R38F	1.75	0.60	0.86
R39F	1.82	0.95	1.16
R40F	1.47	0.94	1.26

Table 13 Summary of Female NHP Test Case Analysis

	Test Cases			
	Absolute Difference Intake (Sum)	Absolute Difference Skeleton (Sum)	Absolute Difference Whole-body (Sum)	Total
ICRP-78 Model	7.45	6.21	7.46	21.12
Male Model from Krage	4.41	4.79	4.36	13.56
Modified Krage Model	4.15	4.62	4.12	12.89

The evaluation of the test cases for intake, skeletal retention, and whole-body retention can be seen in Table 13. It is shown that for the three parameters evaluated, the modified Krage model better predicted the observed data by a factor of 1.64 compared to that of the ICRP-78, model, and 1.05 times better than the male NHP Krage model. ICRP-78 is specifically tailored for predictions of translocation this could explain many of our observations about performance.

5.4 Offspring Evaluation

The products of the evaluation of strontium transfer rates from the mother to the fetus are a set of ratios that vary in time including a C_F:C_M ratio of 0.1 for administration at -52 weeks to 0.2 at 26 weeks provided in Table 14. The change in values is due to the change in time over when the intake was assumed to have occurred. To evaluate the transfer of radionuclides to the offspring from the mother, four cases of NHP mother to offspring via placental transfer were evaluated, data from these are provided in Table 4. The cases encompassed time of exposure to conception of 486 to 2,478 days (69 to 353 weeks) using a 164 day gestation period (Lang, 2005). Calculating the C_F:C_M ratios for

the NHP cases, a value of 0.19 to 0.30 was observed for a ratio of fetus to mother using Equation 2. Further evaluating all the cases as a whole, it is evident the average value for all four of the cases is greater than that suggested by ICRP-88 as shown in Table 13. Human data from Tolstykh et al. shown in Table 15 calculated a C_F/C_M ratio which is normalized for unit mass of calcium (E.I. Tolstykh, 1998). The C_F/C_M ratios show three cases above the ICRP-88 suggested 0.2 C_F:C_M ratio expected at 26 weeks of preconception. Other models and data also suggest a higher value than 0.2 for preconception exposures (NB Shagina T. F., 2015). When comparing the human case values with the present NHP data it is evident that they suggest a range greater than the 0.2 C_F:C_M ratio for preconception. The increase in transfer of material to the fetus suggests that more nutrients from the skeleton of the mother are made available during gestation and transferred across the fetal barrier than previously expected.

Table 14. Placental Transfer of Strontium from Mother to Fetus

Fetus:Mother whole-body concentration ratios at term for intakes of Sr either prior to conception or during pregnancy.					
Fell (1998)		Fell (2001)		ICRP-88	
Time of Intake (Weeks)	CF:CM	Time of Intake (Weeks)	CF:CM	Time of Intake (Weeks)	CF:CM
-52	0.1	-26	0.2	-26	0.2
8	0.5	0	0.3	0	0.3
12	1	10	0.7	10	0.7
24	3	15	2	15	2
30	6	25	4	25	4
36	9	35	8	35	8
8-36 Chronic	5	0-38 Chronic	4	0-38 Chronic	4

Table 15 NHP Placental Transfer

Dam #	Fetus #	Mass of Dam (Kg)	Days Post Exposure to Sacrifice (Dam)	Activity at Sacrifice (Bq)	Days Post Exposure to Birth	Days Post Conception to Sacrifice (Fetus)	Fetal Mass (Kg)	Activity In Offspring (Bq)	(C_F : C_M)
R339F	R440M	5.67	1418	443540	1417	0	0.37	8799	0.30
R21F	R404F	5.9	6449	84927	2642	0	0.6	1648	0.19
R341F	R442M	5.6	1692	493146	688	158	0.5	8192	0.19
R345F	R446F	7.45	1824	331556	650	2	0.5	4854	0.22

Table 16 Human Fetal Transfer from Tolstykh et al.

Identification Code (URCRM Databases)	Mother (Bq/g-Ca)	Fetus (Bq/g-Ca)	Ratio (C_F / $C_{M)}$
11246	51.8	13.69	0.26
7391	26.6	5.55	0.21
194555	36.21	8.8	0.24
80730	219.3	7.03	0.03
155475	117.1	2.37	0.02
379311	45.36	0.56	0.01

a. Values are activity of ^{90}Sr

5.5 Gastrointestinal Absorption

Table 17 gives the known intake, whole-body counting data, and activity residing in the skeleton for optimization case R335F. The activity present in the whole-body counting radioactive strontium determined to be in the body during the first 30 days after exposure leads us to conclude that the feeding was successful. This conclusion is drawn from the knowledge that strontium is assumed to be absorbed rapidly into the bone structure and releases slowly back to the circulatory system. The activity residing in the skeleton of case R335F can also be found in Table 18. It is important to note the case R335F gave birth to an infant at 1,584 days post exposure. The infant R436M, upon analysis was determined to have 0.02% of the initial activity assumed to be consumed by the mother R335F; no attempt was made to account for the activity transferred to the offspring form the mother. Using the Krage NHP model and the default f_1 (f_1 = 0.1 and 0.3) values in in the ICRP 30 gastrointestinal tract model, we have predicted the activity in the body with respect to time in Figure 19. Evaluating Figure 19, it is evident that the shape of the retention in the whole-body fits within the bounds of published literature values. However, neither value of f_1 provides a good fit to the data and the appropriate f_1 value lies in between the two default suggestions. Using the Krage model and the default f_1 (F_1=0.3) in the ICRP 30 gastrointestinal tract model, IMBA calculated an intake of 13.1MBq which did not meet the requirements to predict within 5% for the case to be considered optimized. In response, the f_1 value was modified until a value was determined to be within 5% of the known intake. The final f_1 value was determined to be 0.213 (0.21) as calculated by IMBA resulting in a predicted intake of 18.508 MBq and a 1% difference in prediction. This value of f_1 is considered reasonable, as that reported by

Spencer et al. for strontium transfer from the GI tract to blood was 0.11 to 0.32 (H Spencer, 1957).

Table 17 Case R335F Raw Data

R335F Known Intake 18.5 MBq Skeleton	
Time (Days)	Measured Activity (Bq)
2738	184075

Whole-body Count	
Time (Days)	Measured (MBq)
26	1.943
29	1.584
33	1.536
40	1.656
56	1.375
64	1.469
74	1.437
97	1.421
117	1.071
133	1.114
162	1.236
194	1.062
269	1.053
334	0.944
580	0.894
788	0.690
1272	0.562
1321	0.524
1434	0.505
1714	0.337
1938	0.261
2114	0.244
2364	0.196
2531	0.185
2576	0.235
2738	0.189

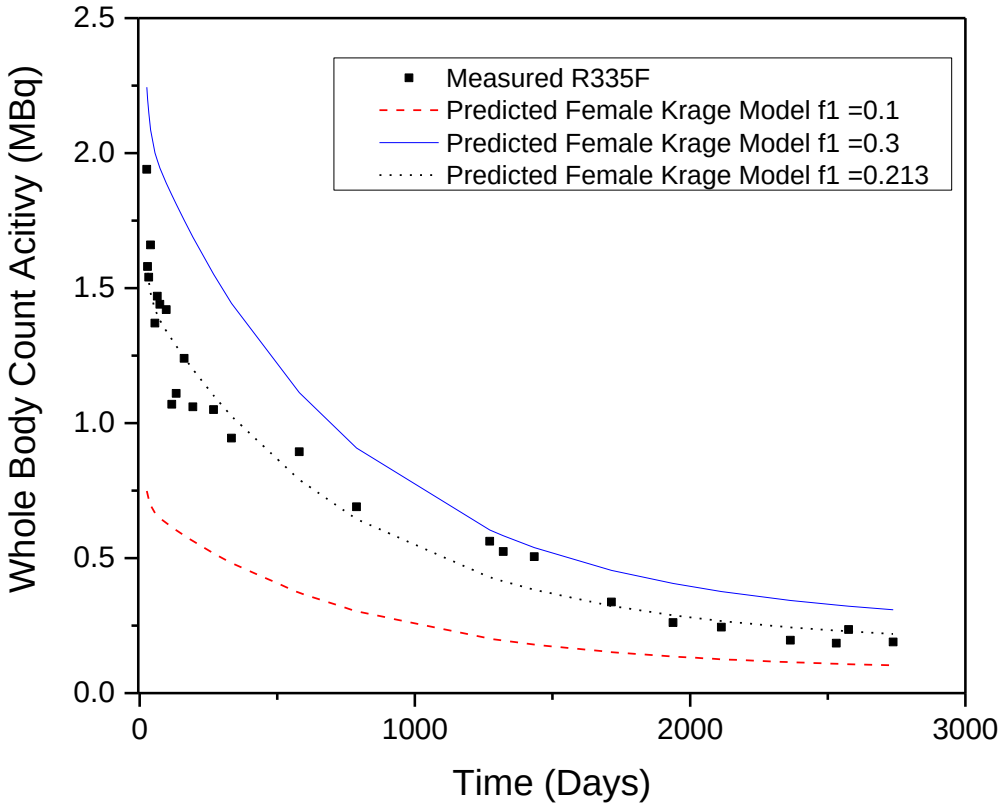

Figure 19 Female Whole-body Count Predictions When Modifying f_1

Using the optimized f_1 value for case R335F two other cases R309F and R347F were tested. In both test cases the subjects had two offspring that were conceived and born during the experiment. The data of the offspring were neglected as they did not pose a significant source of material loss, which at maximum was less than 0.03% of the intake per offspring. Again projecting the data for case R309F shown in Figure 20, we note that the default f_1 values encompassed the measured whole-body retention as desired. Using the optimized f_1 value resulted in a predicted intake of 16.6 MBq corresponding to an

11% difference from the stated value of 18.5 MBq as seen in the data report in Table 18. To predict the skeletal value expected by the Krage and ICRP gastrointestinal tract model at sacrifice the known intake was used to project the amount of activity at 1,274 days. The result of the skeletal prediction at sacrifice showed a 37% over prediction from the known value.

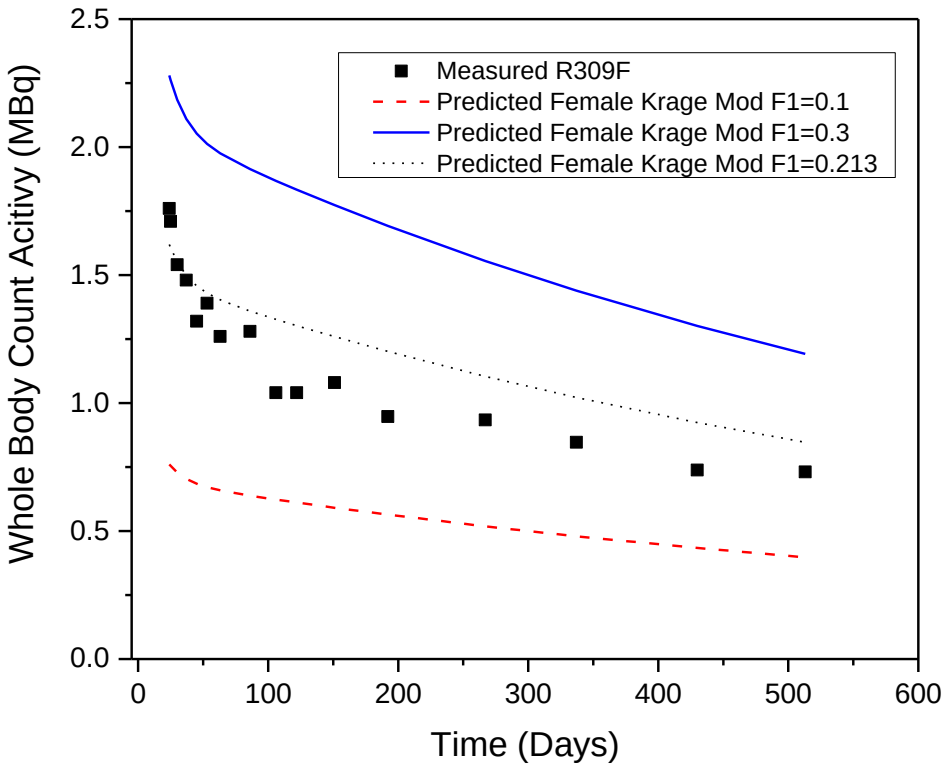

Figure 20 Whole-body Retention of R309F from Ingested Strontium-90

Table 18. Analysis of Known Intake, Whole-body Retention, and Skeletal Retention at Sacrifice Case R309F

R309F Known Intake 18.5 MBq Predicted Intake 16.6 MBq		
Skeleton		
Time	Measured Activity (Bq)	Predicted Activity (Bq)
1274	288600	422360

Whole-body Count		
Time (Days)	Measured (MBq)	Predicted (MBq) f_1 =0.213
24	1.758	1.619
25	1.713	1.606
30	1.537	1.552
37	1.480	1.498
45	1.315	1.458
53	1.386	1.429
63	1.264	1.403
86	1.284	1.359
106	1.040	1.327
122	1.040	1.302
151	1.080	1.259
192	0.947	1.202
267	0.934	1.104
337	0.847	1.022
430	0.738	0.924
513	0.731	0.847

In the analysis of case R347F an f_1 value of 0.213 was used as a transfer rate between the GI tract and the blood was also used. The predicted intake of case R347F as shown in Table 19, predicted an intake of 15.7 MBq, while the known intake of this case was 18.5 MBq. The percent difference of 19% in case R347F is greater than that of case

R309F. Conversely, the predicted activity in the skeleton at sacrifice from the known intake is only 19% which is twice as good of a prediction for case R309F. A comparison of the prediction of the activity residing in the whole-body against the default f_1 values and the optimized value is shown in Figure 21. We can see from the dashed line in the figure that when the known value is input into the model, it over predicts the activity residing in the body on average by 23%. The over prediction of the retention in skeleton model and the under prediction in the known intake can be due to many factors. A possibility that would result in the over prediction residing in the whole-body using the known intake and under prediction of the calculated intake is the uncertainty in the known intake. The intake in this study was not corrected for any surface contamination of the monkey through feeding, nor were the droppings analyzed for strontium activity to correct for the total amount of activity ingested. This leads us to believe that the true intake is not well known for the ingestion; however, the uptake of material behaves as predicted when using the default parameters.

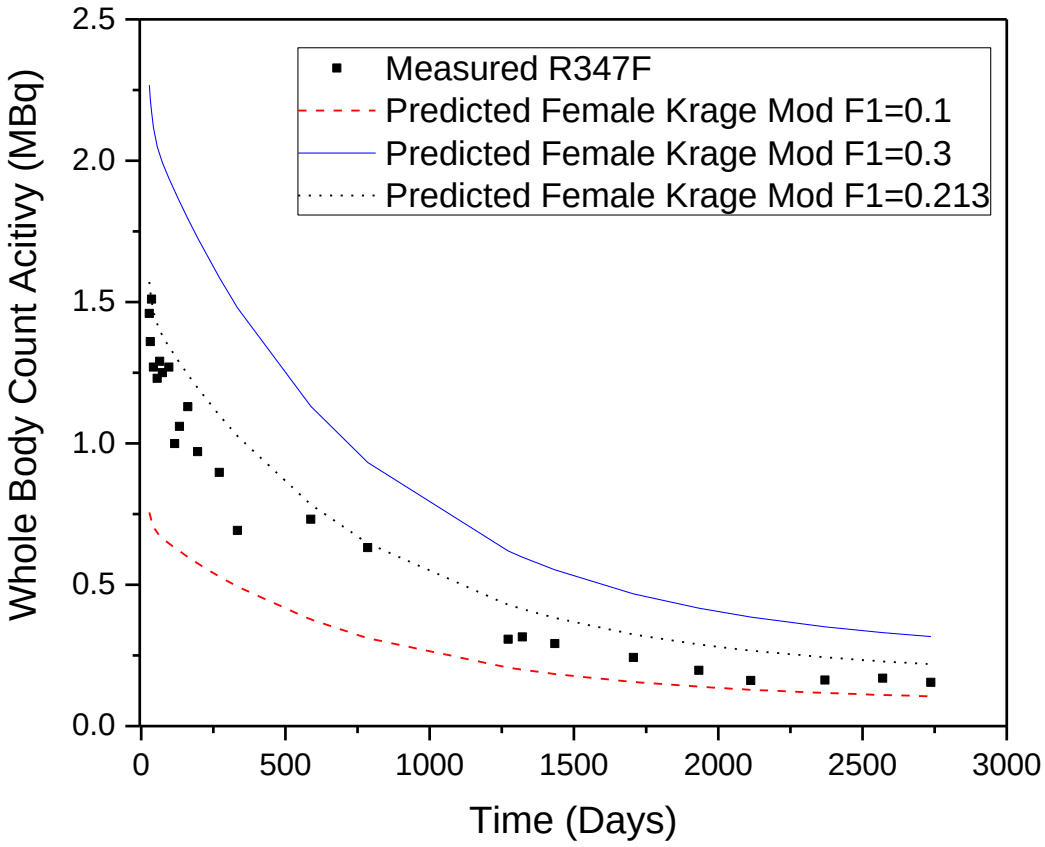

Figure 21. Whole-body Retention of Ingestion Case R335F and Modified f_1 Value Predictions

Table 19. Whole-body Retention and Skeletal Predictions of Case R335F

R347F Known Intake 18.96 MBq Predicted Intake 15.7 MBq		
	Skeleton	
Time	Measured Activity (Bq)	Predicted Activity (Bq)
2737	184075	222270

	Whole-body Count	
Time (Days)	Measured (MBq)	Predicted (MBq) f_1 =0.213
28	1.460	1.610
32	1.357	1.572
36	1.513	1.542
43	1.268	1.503
56	1.234	1.456
64	1.285	1.436
74	1.253	1.415
96	1.274	1.376
116	0.999	1.344
133	1.056	1.318
162	1.134	1.274
196	0.971	1.226
271	0.897	1.127
334	0.692	1.051
588	0.732	0.803
785	0.631	0.663
1272	0.307	0.440
1321	0.315	0.424
1434	0.292	0.392
1706	0.243	0.332
1933	0.197	0.296
2113	0.161	0.274
2370	0.163	0.249
2570	0.169	0.235
2737	0.155	0.225

Chapter 6 SUMMARY AND CONCLUSIONS

6.1 Hypothesis Summary

In testing the robustness of the ICRP Publication 78 ^{90}Sr systemic model, the systemic model did not accurately predict the intake from the composited primate bioassay data within 10%. The failure of the ^{90}Sr model to predict within 10% lead to the acceptance of the alternate hypothesis $H_{1, A}$. The support of the alternate hypothesis suggests that the intake prediction cannot be scrupulously predicted by the default ICRP No. 78 ^{90}Sr systemic model parameters.

Through the modification of the ICRP Publication 78 biokinetic three models were developed and tested on the male cohort of monkeys. The predicted activity in skeleton and intake was analyzed to determine which model was most accurate when comparing the three models. Model A, did not meet the selection criteria and was rejected. The other two models, however, did make it into the testing phase. The result of the testing lead of the alternate hypothesis $H_{2, A}$ being supported such that the activities predicted in skeleton and intake appeared to be about 10% better than that of the default model while evaluating these data sets. The acceptance of the alternate hypothesis implies that the skeletal prediction and intake can be improved by altering the default model parameters. Further testing was then carried out to determine which model was better able to predict as a whole.

The predicted injected activity was compared between the default and optimized model to test subjects that were independent of those used in to optimize the default

model. The majority of female cases showed a more accurate prediction than the default model by approximately 10% or greater. This improvement in prediction by the altered parameters can be used to predict the injected activity of subjects with similar injected activity, lead to the acceptance to the alternate hypothesis $H_{3,\,A}$. The support of the alternate hypothesis suggests that the intake prediction can be improved by the optimized model for the female cohort.

The 4th hypothesis was concerned with the validity of the optimized transfer rates for Male and Female NHP systemic models and the ICRP 30 predictive capability for ingestion cases. It was determined using either of the default f_1 (f_1 0.1 or 0.3) values that neither were able to predict ingested activities to within 20%. However, the two values of f_1 did encompass the true data and it was determined that modification of the f_1 would improve the prediction capabilities of the model.

6.2 Model A, B, C for Male Nonhuman Primate Summary

The default ICRP 78 ^{90}Sr hermaphrodite model was used to predict the intake for a composite cohort of male nonhuman primates. When comparing the ICRP 78 predictions to the known intake, it demonstrated a 180% difference for the male cohort. When evaluating the ICRP systemic model against independent test cases, the model showed the best predictions for subjects with short-time to sacrifice. There existed a discrepancy between the predicted and measured values for the composite cohort and a majority of the independent test cases, this implied to us that changes in the biokinetic model could improve model predictions for nonhuman primates.

Therefore, three biokinetic models were developed; model A, B, and C, for estimating strontium intakes and retention in skeleton from a known intake. Evaluating the Monte Carlo analysis for the models resulted in rejecting model A as a possible model based on the parameter selection criteria. Furthermore, through comparison of model B with model C, it was evident that model C was a better fit to the composite data by a factor of three. Finally in comparing model C with the ICRP systemic model for strontium, it was inferred that model C had better prediction capabilities overall when compared to the systemic model by a factor of two. Although, there exists some deviation in specific test cases, this may be explained by the short time to sacrifice of the test subjects. Therefore, it is suggested that model C might be used to better predicted activity in the skeleton in the long term at least for nonhuman primates. However, recommendations presented in this work are not intended to conflict with current practice, rather to provide additional insight into strontium biokinetics.

6.3 Female Biokinetic Model Evaluation and Placental transfer

The default ICRP 78 ^{90}Sr hermaphrodite model produced predictions of intake with a 10% difference from measured value of the NHP composite cohort. The discrepancies between predicted and measured values for the composite predictions and the majority of the independent test cases implied to us that changes in the biokinetic model at might improve the bioassay predictions for NHP. Similar to the case of male NHP, the ICRP 78 model predicts bone and intake well often within 5% and 35% respectively for short periods of time between intake and sacrifice when evaluating NHP cases.

Two additional biokinetic models for strontium transfer in NHP were tested. The models tested included a NHP model developed for males by Krage and a model in which the Krage transfer rate were modified. The modified Krage model was optimized by varying the bone compartment transfer rates to better predict the strontium intake, whole-body activity, and activity in skeleton at sacrifice. To further evaluate the predictive capabilities of the optimized model, it was tested on 6-female test cases. When comparing the predictions of the Krage, modified Krage, and ICRP 78 model; it was shown that the modified Krage model predicted better by 0.67 when comparing the absolute differences for strontium intake, whole-body activity, and activity in skeleton at sacrifice with the Krage model.

Transfer rates for strontium translocation in the pregnant NHP were compared against ICRP 88 and current literature values. The results of this comparison suggest that ICRP 88 for NHP under predicts the activity transferred to the fetus from preconception exposures of ^{90}Sr. When comparing the NHP transfer coefficients to human cases in the published literature, it is shown that these transfer rates agree. Therefore, the adoption of a new model for strontium transfer to the fetus for preconception exposures could provide better estimates of activity transferred to fetal tissues from strontium isotopes. It is suggested that recommendations presented in this work are not intended to conflict with current practice, rather to provide additional insight into strontium biokinetics.

6.4 The Behavior of Strontium-90 in Female Nonhuman Primates Following an Oral Ingestion

A special nonhuman primate model developed by Krage was used for the reconstruction of ^{90}Sr-intake for three NHP cases. Only data on ^{90}Sr in whole-body and activity residing in the skeleton was applied for the reconstruction. It should be noted that all cases were female and each of them had one or two offspring, and data from the fetus was not used in assessment of the ^{90}Sr intake or whole-body retention.

With regard to intake prediction, two methods of estimation were used; whole-body counting and skeletal analysis. It is of interest to compare the predicted intake for the modified $f_1 = 0.213$ compared to the measured value and compare the difference. In both test cases R309F and R347F the intake was under predicted by at least 11%. This difference albeit not significant in the context of internal dosimetry does raise the question as to the accuracy of the known intake.

As for the interpretation of the results of the skeletal uptake, at least two processes will be considered for the discrepancy in prediction. The most significant source of this error is likely due to the uncertainty with the known intake. If the known intake is less than that stated in the data as previously discussed; then the predicted activity in skeleton would be closer to the measured value. Another possibility is that the birth of offspring had a more important effect than would be expected on the skeletal retention. Interpreting all of the data, it is evident that the using the Krage nonhuman primate model and the ICRP 30 gastrointestinal tract model ($f_1 = 0.213$) does a sufficient job (~20%) predicting the activity in the skeleton of monkeys.

6.5 Future Work

Future work regarding ^{90}Sr and nonhuman primate research using the data provided to Idaho State University of work performed by Patricia Durbin and her colleagues should be focused on examining transfer of material from the mother to the offspring and the few cases of detailed bone dissection. The framework to carry out such a detailed and complex analysis of transfer pathways to offspring should focus on rhesus macaque developmental biology. Focusing on transfer in this manner will allow for proper corrections when discussing nutrition needs of the animals. However, it should be noted that data is limited for this specific work and may result in a qualitative result instead of a desired quantitative result. Detailed bone analysis could prove useful in justifying a split of bone into cortical and trabecular compartments; however, there currently does not exist an accurate description of how the bones were broken down and evaluated.

Progressing with the research presented in this dissertation the proposed models presented should be examined on human subjects. Limitations currently preventing this scope of work are the inability to test human subjects and the lack of accidental exposure data.

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